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THE BLOOD PRESSURE REDUCING PROPERTY OF EXTRACTS OF KIDNEYS IN HYPERTENSIVE PATIENTS AND ANIMALS *

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1. TIGERSTEDT and Bergmann [1] demonstrated that bilateral nephrectomy increases the rise in arterial pressure occurring in anesthetized animals when extracts of kidney containing renin are injected into them. This observation was confirmed by Merrill, Williams and Harrison,[2] and by Fasciolo, Houssay and Taquini [3] who suggested that the increased sensitivity might be due to loss of an anti-pressor substance. Similar increase in sensitivity was observed by Page and Helmer [4] when angiotonin was administered instead of renin. Angiotonin is the pressor substance resulting from interaction of renin and renin-activator.[5]

Nephrectomy therefore appears to remove the source of some substance which opposes the pressor action of angiotonin.

2. Removal of the normal kidney when the artery of the opposite one is constricted by a clamp or the parenchyma compressed by a perinephric scar, intensifies the hypertension. To explain this, Blalock and Levy [6] suggested that the normal kidney may destroy the pressor substance causing the hypertension. Fasciolo [7] shortly thereafter demonstrated that the rise in pressure was more rapid, reached greater heights and was more permanent when the Goldblatt clamp was applied to the remaining kidney in a dog which had been uninephrectomized. He also demonstrated that normal kidneys opposed the action of a hypothetical pressor substance by showing that a greater rise in arterial pressure occurred in nephrectomized dogs than in normal ones when blood perfusing an ischemic kidney was allowed to enter their circulation.

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Katz, Friedman, Rodbard and Weinstein [8] formulated the belief that the intensity of the hypertension depends on the presence of normal renal tissue. They suggested that there is a direct relationship between the height of the blood pressure and the ratio of "ischemic" to normal tissue and that the antagonistic action of normal renal tissue is due to its metabolic and not its excretory activity.

3. Plasma from animals in which sufficient amounts of renin were injected to cause them no longer to respond with rise in arterial pressure (tachyphylaxis) does not cause vasoconstriction in the isolated rabbit's ear when perfused with added renin (Page [9]). More important, even the addition of renin-activator does not impart vasoconstrictor properties. Contrariwise, normal blood with added renin causes marked vasoconstriction. Administration of renin thus appears to cause the release of a substance in the intact animal which antagonizes renin or its reaction product, angiotonin. On this basis our conception of anti-pressor substances arose.

4. Plasma of nephrectomized animals when mixed with angiotonin and renin and perfused through a rabbit's ear causes much greater vasoconstriction than normal plasma (Page and Helmer [4]). The removal of the kidneys has thus removed the factor which opposes the action of angiotonin. This factor is evidently humoral since it can be transferred from the intact animals to the isolated perfused rabbit's ear.

5. Hypersensitivity to the pressor action of angiotonin and renin induced by nephrectomy can be temporarily abolished by transfusion of large amounts of normal blood into the nephrectomized animal. Normal blood, therefore, contains an inhibitor substance.[4] According to Freeman [10] direct transfusion of from 25 to 200 c.c. of normal blood into hypertensive dogs produces a fall in pressure ranging from 6 to 25 per cent lasting 6 to 31 minutes. Blood from normal and hypertensive human donors transfused into normal and hypertensive recipients respectively caused no fall in arterial pressure.

6. Renal extracts have been prepared which, when given by mouth, diminish partially the response of normal rats to the pressor action of renin, ephedrine and pitressin.[11] The increased sensitivity of nephrectomized dogs to angiotonin and renin can be abolished by parenteral injection of renal extract.[12]

These observations suggested that a substance is contained in renal tissue which might oppose the pressor action of angiotonin or similar pressor agents and result in reduction of arterial pressure. Attempts to extract such an inhibitor or antipressor substance have, we believe, been successful both in the hands of Grollman, Harrison and Williams,[13] and in ours.[14] The evidence at present available indicates that we are dealing with the same principle as that reported shortly before by Harrison, Grollman and Williams. (Our work was based on different reasoning and was done independently. The two groups are now collaborating toward a further solution of the problem.) It is of great interest that their material is active by mouth in

rats, dogs and man, most of their best results having been obtained by this mode of administration. Our work has been limited to parenteral methods of administration.

Preparation of Renal Extracts

Methods for the preparation of these extracts have already been published by Grollman, Williams and Harrison [15] and by us.[16, 17] In principle, the method we have employed consists of extraction of ground fresh kidneys with acetic acid—salt solution, heating the mixture to 56° C. and precipitating the filtrate with ammonium sulfate between 0.25 and 0.6 saturation. This precipitation is repeated twice and the product dialyzed free of ammonium sulfate. Extraction of this product with ether to remove lipids appears to decrease the number of reactions produced and certainly reduces the local tissue irritation. This step had not been previously employed. It is then sterilized by filtration through a Seitz filter.

The Effect of Injection of Renal Extracts in Hypertensive Dogs

Dogs were made hypertensive by the silk perinephritis method.[18] Blood pressure was measured daily by direct femoral intra-arterial puncture, and the pressure recorded on a smoked drum from a mercury manometer. When the mean arterial pressure was over 180 mm. Hg, and remained steadily above this figure for a week, the dog was used for assaying the potency of the renal extracts.

It was found convenient in the preparation of hypertensive animals to wrap the left kidney in silk and remove the other kidney at the same time. In alternate animals, both kidneys were wrapped in silk. The blood pressure in the animals in which one kidney has been wrapped in silk and the other kidney removed usually rises more rapidly and to more extreme heights. The incidence of the malignant syndrome is greater among them. The blood pressure in the second group rises more slowly and tends to remain more steadily at the elevated pressure without as frequent complication by the appearance of the malignant syndrome. Both types of hypertension are useful for assay purposes. Two hundred and eighty hypertensive dogs have been treated with renal extracts.

Extracts were usually injected subcutaneously. In dogs they cause little local reaction and no general ones. No immediate change in arterial pressure is observed. In from two to four days the fall begins and its rapidity depends in large measure on the amount of extract given.

Extract prepared from 400 to 900 grams of fresh pork kidney is usually required to reduce the blood pressure of a 12 kilo dog from 200 to 130 mm. Hg. If much larger doses are given a shock-like syndrome appears which has been well described by Harrison, Grollman and Williams.[11] The animal loses its appetite, becomes weak, and tachycardia appears. This is followed,

after the blood pressure has fallen to 70 mm. Hg or lower, by oliguria or anuria, bloodlessness of the extremities, and elevated blood urea nitrogen.

The fall in arterial pressure is usually gradual if the extract is given in moderate doses daily, the pressure reaching normal or near normal levels in five to eight days. If the extract is now discontinued the blood pressure may remain low for several days and in unusual cases for weeks and gradually rise to its original hypertensive level. Some dogs require more extract to reduce this blood pressure than do others. This phenomenon does not ap-

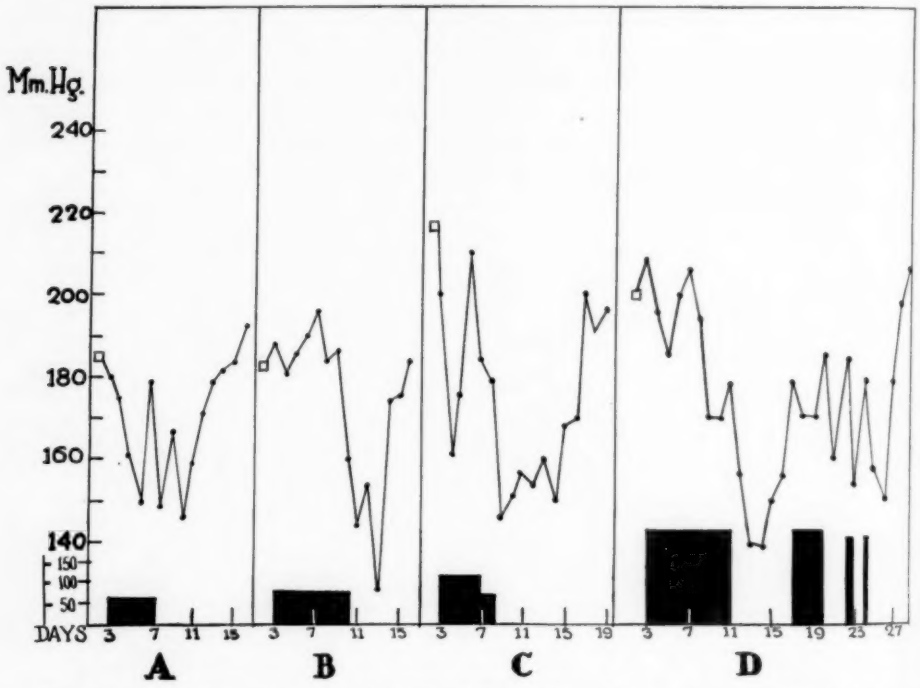


FIG. 1. *Dog 5–87.* Female, weight 10.2 kilos. The effect of four renal extracts on arterial pressure. Arterial pressure is expressed in mm. Hg (ordinate) and time in days (abscissa). □ represents the average arterial pressure during 10 days before extract was given. Daily dosage of extract is expressed by height of shaded area (ordinate) as grams of kidney used in preparation of extract and given per kilo of body weight.

A—Renal extract prepared by 0.3 to 0.8 saturation with ammonium sulfate. Hypertension had been present 3 months before extract was administered.

B—Renal extract prepared by extraction at pH 4.0 with 2 per cent saline and heated to 56° C. Filtrate saturated with ammonium sulfate and precipitate dissolved in water and dialyzed. An interval of 7 months elapsed between *A* and *B*.

C—Renal extract prepared by twice precipitating with ammonium sulfate and treatment with barium hydroxide and dialysis. An interval of 5 months elapsed between *B* and *C*. Blood urea nitrogen, on fourth day extract was given, was 17 mg. per 100 c.c. Day after administration of extract was completed and when maximum reduction of blood pressure was observed, blood urea nitrogen was 21 mg. per 100 c.c.

D—Renal extract was from pooled lot of extracts which had been prepared by precipitating three times with ammonium sulfate. An interval of 4 months elapsed between *C* and *D*. Blood urea nitrogen on first day of administration of this extract was 70 mg. per 100 c.c.; on the last day of administration of extract, blood urea was 147 mg. per 100 c.c. Four days after extract had been stopped blood urea nitrogen was 71 mg. per 100 c.c.

TABLE I

The Effect on Blood Urea Nitrogen of Reduction of Arterial Pressure by Kidney Extract in Hypertensive Dogs

Dog. No.	Before Renal Extracts		Maximum Reduction of Arterial Pressure					Effect of Spontaneous Return of Arterial Pressure to Hypertensive Levels		
	Arterial Pressure mm. Hg	Blood Urea Nitrogen in mg./100 c.c.	Arterial Pressure mm. Hg	Blood Urea Nitrogen in mg./100 c.c.	No. Days to Reduce Arterial Pressure	Evidence of Malignant Hypertension		Arterial Pressure mm. Hg	Blood Urea Nitrogen in mg./100 c.c.	No. Days Required for Rise in Arterial Pressure and Change in B. U. N.
						Bloody Diarrhea	Retinal Detachment			
Group I. No Significant Change of Blood Urea Nitrogen or Fall										
8–76	224	24	96	26	2	—	—	178	29.8	30
	216	28.6	146	24.2	11	—	bilateral	208	58.7	13
9–38	180	44.5	164	27	6	+++	—	204	71.5	3
12–37	212	49.6	156	14.2	3	+++	bilateral	174	22.9	3
10–21	210	34	154	18.6	4	—	—	210	—	—
12–80	184	14.1	144	11.4	7	—	—	166	—	—
11–78	208	32.6	140	27	2	—	+	224	—	—
13–22	200	18	140	12.8	7	+	unilateral	188	—	—
9–80	188	17	150	22.8	5	—	bilateral	178	21.4	5
10–21	206	31	138	36	2	—	—	210	34	12
Group II. Significant Rise in Blood Urea Nitrogen										
13–05	180	28.6	142	53.8	2	—	bilateral	166	49.5	3
12–24	192	15.6	98	136	5	+	bilateral	190	42.5	6
7–52	200	49	80	112	4	+++	++	—	—	—
7–83	230	25.4	124	75	2	—	—	178	29.7	8
5–87	208	69	140	147	2	—	—	166	71.5	4
8–76	224	20	138	37	4	—	—	160	38	5

pear to be directly related to the initial height of the blood pressure. It is for this reason that three or more dogs may be required for the assay of each extract.

The effect on renal function is often striking. Corcoran and Page[19] found that injections of inhibitor into normotensive dogs caused relaxation of the glomerular efferent arteriole and usually an increase in renal blood flow. No change in blood pressure occurred in these animals unless very large doses were given. In hypertensive dogs reduction of blood pressure to levels of about 150 mm. Hg was associated initially with rise in blood flow but if the pressure continued to decline, the blood flow fell precipitously to return to higher levels as arterial pressure increased. Renal extracts thus appeared to oppose the renal action of substances such as angiotonin, for it had been shown[20, 21] that angiotonin sharply reduced blood flow chiefly by constricting the glomerular efferent arterioles.

The effect on blood urea nitrogen is variable (table 1). The more usual effect is a fall, but no significant change may occur. The less usual is a

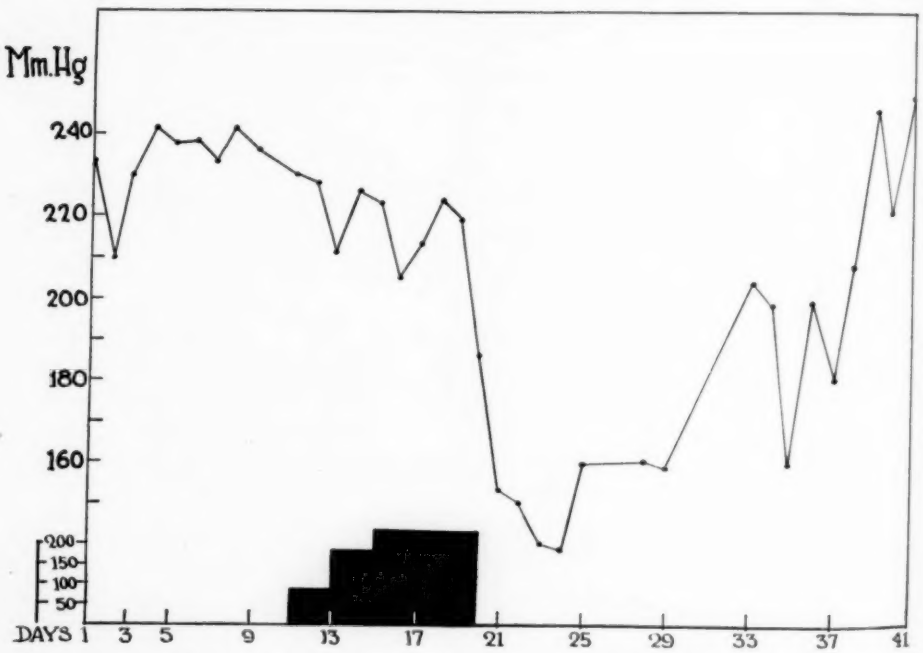


FIG. 2. *Dog. 8–76.* Weight 9.2 kilos. The effect on arterial pressure of renal extract prepared by precipitation with ammonium sulfate and treatment with barium hydroxide and dialysis. Arterial pressure is expressed in mm. Hg (ordinate) and time in days (abscissa). Daily dosage of extract is expressed in grams of kidney used in its preparation and given per kilo of body weight and is represented in the figure by height of shaded area (ordinate). Hypertension had been present five months. During last three months retinal hemorrhages and detachment were observed while animal received six different kidney extracts. The results produced by the seventh extract are shown in the figure. Blood urea nitrogen on second day extract was administered was 20 mg. per 100 c.c.; on last day of administration it was 22 mg. per 100 c.c. Three days after extract was stopped blood urea nitrogen was 37 mg. per 100 c.c. and eleven days later it was 38 mg. per 100 c.c.

pronounced rise in blood urea which falls again when the arterial pressure spontaneously resumes its hypertensive level. There appears to be no relationship between these changes and the occurrence of the malignant syndrome.

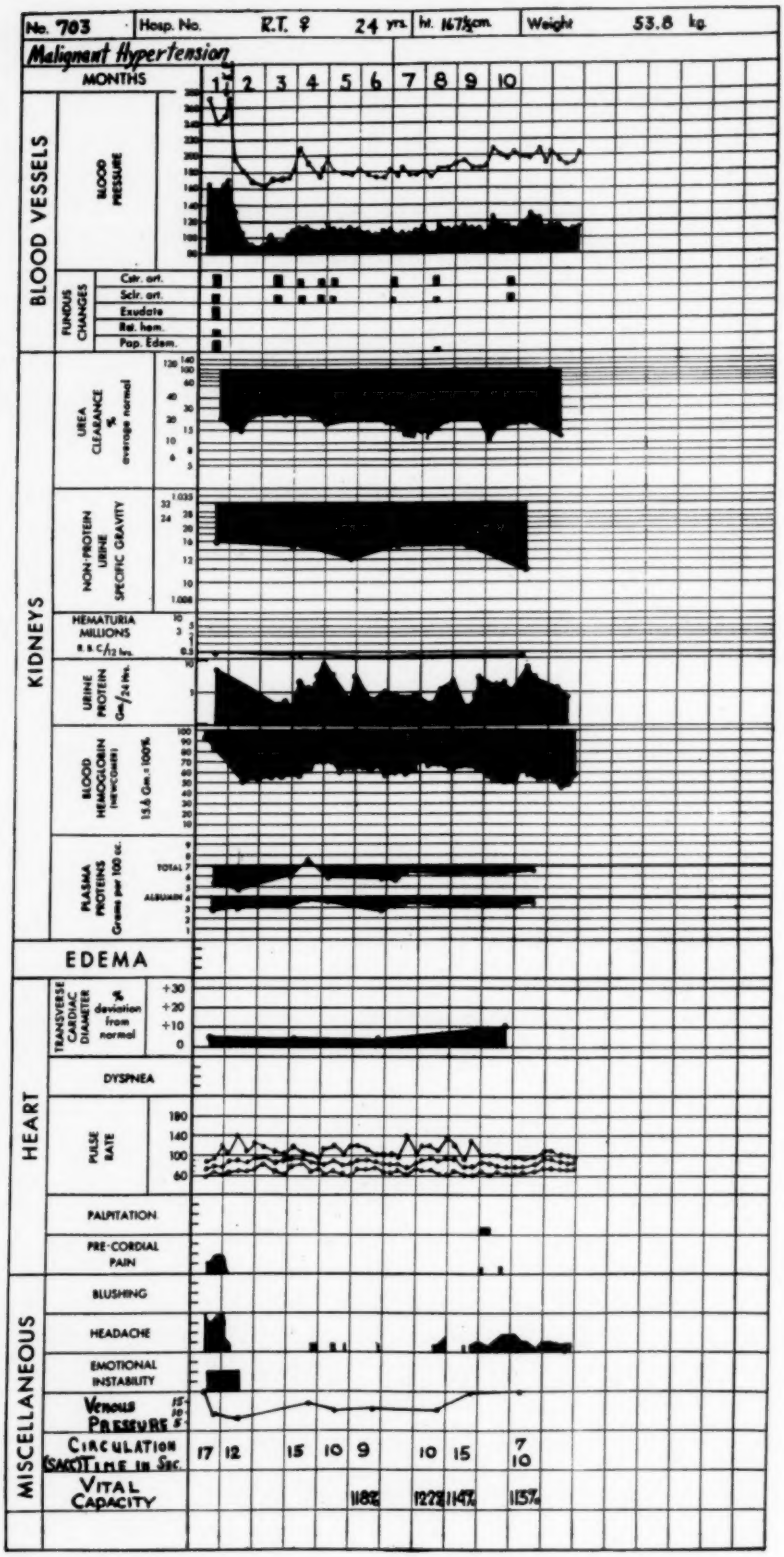
Many of the dogs with experimental hypertension exhibit the malignant syndrome. This consists of loss of appetite, early blindness with detachment of the retina, papilledema and massive intra-ocular hemorrhages. The animals become weak, have severe bloody diarrhea, vomiting, pulmonary edema, hematuria, anuria, rapidly progressive anemia, and convulsions. Death usually occurs within several days, but in unusual cases it may be much longer. If treatment is not started too late, many of these animals can be saved. The syndrome often reappears when the injections of inhibitor are discontinued and may again be counteracted by further administration of kidney extract. The blood urea nitrogen, which usually is initially very high, usually falls as the blood pressure falls and clinical improvement occurs. Vision returns, associated with reattachment of the retina, subsidence of the papilledema and resorption of the hemorrhages. Regression of the other signs such as bloody diarrhea is clearly evident. Much the same results have been obtained in rats with experimental hypertension. They too exhibit the malignant syndrome, and its reversal is also observed when inhibitor is injected.

Effect of Renal Extracts on Patients

The history and certain laboratory data are presented in the following abstracts. The figure which accompanies each abstract is a bedside chart and exhibits in graphic form the most pertinent of the observations made on the patients. It is important for the reader to have a clear notion of the way in which they are prepared to avoid misinterpretation.

An attempt is made when it appears to have any chance of success of estimating the length of time the hypertension has existed, and this is represented by the figures in the line parallel with the word "Months." The blood pressure measurements are usually single determinations until the patient either entered our clinic or was admitted to the hospital. After admission, the patient was put to bed and the arterial pressure was measured twice daily. The blood pressure readings are averaged over a period of a week. One dot on the chart represents such an average. Where such average pressures begin on the chart can be ascertained by noting when urea clearance was determined. It is rare that the patients were not allowed up after a week or more of treatment and in most cases they were transferred to the out-patient department. For this reason the control blood pressure levels taken at complete bed rest should be abnormally low compared with the level taken when the patient is either up and about or outside the hospital.

Fundus changes are indicated under the following headings, employing a semi-quantitative scale of + to ++++ to grade them: (1) arteriolar constriction, (2) arteriolar sclerosis, (3) exudates, (4) retinal hemorrhages,


No. 703
Hosp. No.
R.T. ♀
24 yrs.
ht. 167½cm.
Weight 53.8 kg.
Malignant Hypertension
MONTHS
1 2 3 4 5 6 7 8 9 10
BLOOD VESSELS
BLOOD PRESSURE
FUNDUS CHANGES
Cav. art.
Sclr. art.
Exudate
Ret. hem.
Pap. Edem.
KIDNEYS
UREA CLEARANCE % average normal
NON-PROTEIN URINE SPECIFIC GRAVITY
HEMATURIA MILLIONS R.B.C./12 hrs.
URINE PROTEIN Gm./24 Hrs.
BLOOD HEMOGLOBIN (newcomer) 15.6 Gm.=100%
PLASMA PROTEINS Grams per 100 cc.
TOTAL
ALBUMIN
EDEMA
HEART
TRANSVERSE CARDIAC DIAMETER % deviation from normal
+30
+20
+10
0
DYSPNEA
PULSE RATE
180
140
100
60
PALPITATION
PRE-CORDIAL PAIN
MISCELLANEOUS
BLUSHING
HEADACHE
EMOTIONAL INSTABILITY
Venous Pressure
CIRCULATION (SACC) TIME IN Sec.
17 12 15 10 9 10 15 7/10
VITAL CAPACITY
1188 1222 1147 1157

and (5) papilledema. Urea clearance, as determined by the modification described by Van Slyke, Page, Hiller, and Kirk[22] of the original method, is expressed as average per cent of normal. The ability to concentrate urine maximally is ascertained by withholding water from the patient for 24 hours and measuring the specific gravity of the urine passed after the last 12 hours. Correction is made for the gravity contributed by protein in the urine. Hematuria is determined by counting the red cells in the urine according to the technic of Addis.[23] Values above 500,000 in a 12 hour specimen are considered abnormal. Plasma proteins were determined by the method of Howe.[24] The black areas representing edema have the following significance: Height of black area in quarters of total space (1) trace, (2) moderate pitting, (3) marked pitting, (4) general edema with ascites. The transverse cardiac diameter is recorded as the per cent deviation from normal according to the table of Ungerleider and Clark. The circulation time was determined by intravenous injection of 2.25 gm. of soluble saccharin in 5 c.c. of distilled water. The arm-to-tongue time is measured in seconds. The normal range is considered from 7 to 10 seconds and borderline normal from 10 to 20 seconds. Venous pressure is recorded in centimeters of blood. The thiocyanate content of the blood was ascertained by the method of Crandall and Anderson,[25] and recorded as mg. in 100 c.c. of blood.

Malignant Hypertension

Case Reports

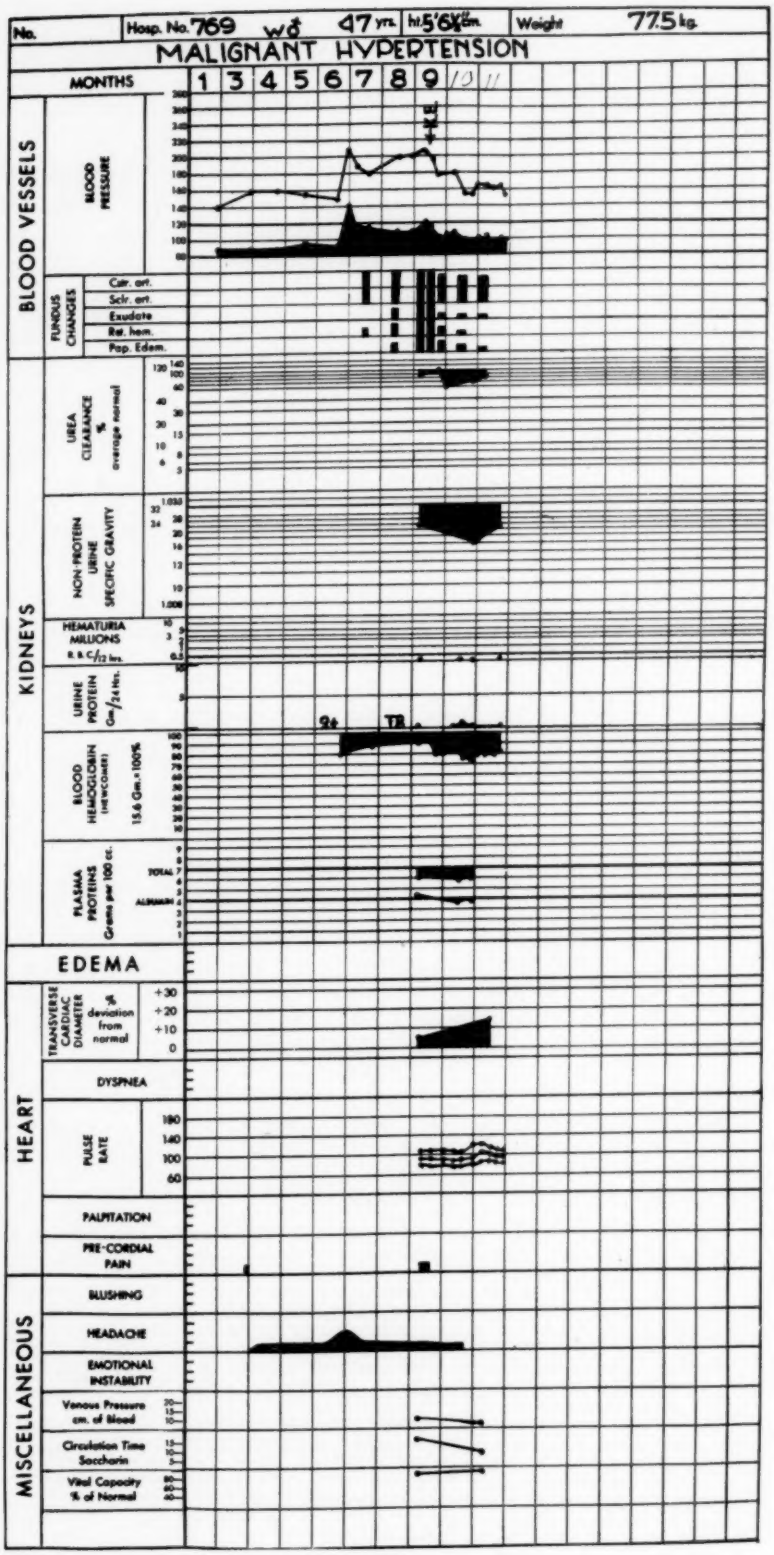
Case 1. R. T. (703). This 24-year-old man complained of severe headaches and blurring of vision. At 12 years of age he had scarlet fever. During the preceding winter he had headaches regularly. Two weeks before admission he fell and hit the back of his head. A severe headache immediately occurred and persisted. At this time his blood pressure was found to be elevated. Vision in the left eye rather suddenly became so poor that he was unable to read, and the vision in the right one seemed to be deteriorating.

The patient appeared acutely ill; his face was drawn and anxious. The right side of his face twitched. A subconjunctival hemorrhage was seen in the right eye. Grade 3 papilledema, grade 4 exudates, grade 2 hemorrhages, and grade 3 constriction were observed in the eyegrounds. The heart was slightly enlarged (+5 per cent deviation). Venous pressure was 22 cm. in terms of normal salt. The electrocardiogram showed inversion of the T-waves in Leads I, II, III, and IV.

The clinical improvement in this man was remarkable. Shortly after admission acute glaucoma occurred. Reduction of the blood pressure by kidney extract appeared to aid in resolution of the process.

This patient has remained hospitalized for economic reasons, but is up and about. Optic fundi now reveal grade 2 constriction and sclerosis of the retinal arterioles. Electrocardiogram exhibits upright T-waves in all leads. He has been treated with kidney extract continuously for the past 11 months.

Case 2 (769). The arterial pressure of this 47-year-old white male was found to be 140 mm. Hg systolic and 90 mm. diastolic seven months ago. Five months ago it was 160 mm. Hg systolic and 90 mm. diastolic. He complained of headaches, convulsive seizure with loss of consciousness, and almost complete blindness.


No.
Hosp. No. 769
wd
47 yrs.
Weight
77.5 kg.
MALIGNANT HYPERTENSION
MONTHS
1 3 4 5 6 7 8 9
BLOOD VESSELS
BLOOD PRESSURE
FUNDUS CHANGES
Cstr. art.
Sclr. art.
Exudate
Ret. hem.
Pap. Edem.
KIDNEYS
UREA CLEARANCE % average normal
NON-PROTEIN URINE SPECIFIC GRAVITY
HEMATURIA MILLIONS R. B. C./12 hrs.
URINE PROTEIN Gm./24 Hrs.
BLOOD HEMOGLOBIN (HELLIGE) 15.6 Gm. = 100%
PLASMA PROTEINS Grams per 100 cc.
TOTAL
ALBUMIN
EDEMA
HEART
TRANSVERSE CARDIAC DIAMETER % deviation from normal
+30
+20
+10
0
DYSPNEA
PULSE RATE
180
140
100
60
PALPITATION
PRE-CORDIAL PAIN
MISCELLANEOUS
BLUSHING
HEADACHE
EMOTIONAL INSTABILITY
Venous Pressure cm. of Blood
Circulation Time Saccharin
Vital Capacity % of Normal
Rad
TB

Physical findings at the time of admission to the Lilly Clinic were arterial blood pressure 200 mm. Hg systolic and 120 mm. diastolic; ocular fundi revealed grade 4 constriction and sclerosis of retinal vessels; grade 4 hemorrhages, exudates, and papilledema.

Urea clearance was 90.5 per cent of average normal; maximal ability to concentrate urine was 1.023; electrocardiogram was normal.

Arterial blood pressure average for first week at bed rest was 208 mm. Hg systolic and 121 mm. diastolic. Kidney extract was administered intramuscularly. The arterial blood pressure averaged 197 mm. Hg systolic and 115 mm. diastolic for first week of treatment. He was treated for eight weeks, and the blood pressure now averages 166 mm. Hg systolic and 99 mm. diastolic. He now reads newspapers and is symptom free. Ocular fundi show grade 3 constriction and sclerosis; grade 1 exudates and hemorrhages; and grade 2 papilledema.

He has had two shock-like reactions and one bout of chills and fever.

Case 3. M. B. (764). A colored, 35-year-old female complained of protracted headaches, nausea and vomiting, blurring of vision, and dyspnea. Hypertension was discovered five years ago.

On admission to the Lilly Clinic arterial blood pressure was 260 mm. Hg systolic and 140 mm. diastolic. Retinal vessels displayed grade 4 constriction and sclerosis. Ocular fundi revealed grade 3 hemorrhages, grade 1 exudates and papilledema. Heart was enlarged to 11 cm. to left of midline. There was a soft systolic blow at the cardiac apex.

Urea clearance was 44.9 per cent of average normal; maximal ability to concentrate urine was 1.020; proteinuria amounted to 0.8 gm. per 24 hours; blood hemoglobin was 70 per cent of average normal. Retrograde pyelograms were negative. The electrocardiogram displayed left axis deviation, biphasic T-waves in Leads I, II, and IV.

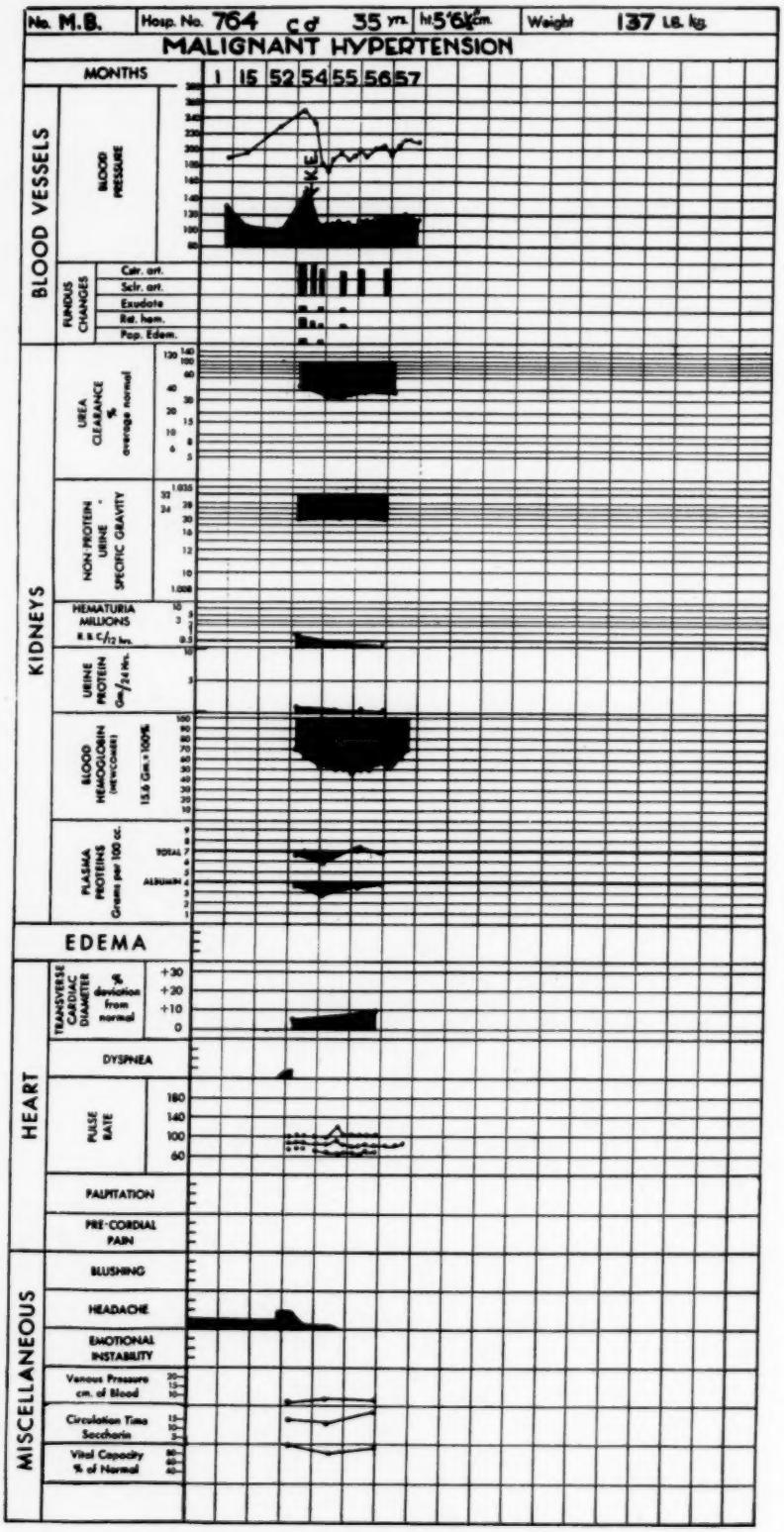
Arterial blood pressure averaged 235 mm. Hg systolic and 137 mm. diastolic for the first week in the hospital. Kidney extract was administered. The arterial blood pressure average for the first week of treatment was 200 mm. Hg systolic and 115 mm. diastolic. This was maintained at a slightly lower average of 187 systolic and 110 mm. diastolic. She became symptom free. The eyegrounds revealed grade 3 constriction and grade 4 sclerosis of retinal vessels. Hemorrhages, exudates, and papilledema entirely disappeared. T-waves in Leads I, II, and IV of electrocardiogram became upright.

This patient suffered one shock-like reaction and almost weekly chills and fever.

Case 4. C. R. (671). A colored female, aged 36, complained of headaches, failing vision, and nocturia of about 10 months' duration. These symptoms progressed until she was unable to read.

Grade 2 arteriosclerosis and constriction of the retinal arterioles were found and grade 2 papilledema. Blood pressure was 256 mm. Hg systolic and 152 mm. diastolic. Grade 1 edema was present. Urea clearance had already fallen to 30 per cent of normal and was continuing to fall. The Addis count revealed a marked increase over normal of the red blood cells in the urine. The cardiac diameter showed + 14 per cent deviation from normal. The electrocardiogram exhibited isoelectric T-waves in Leads I and II (Feb. 28, 1940), which eight days later became inverted.

While resting in bed the blood pressure averaged 233 mm. Hg systolic and 140 mm. diastolic. Retinal hemorrhages were appearing in crops. Beef muscle extract was administered intramuscularly and the blood pressure fell to 188 mm. Hg systolic and 118 mm. Hg diastolic. After discontinuing this extract the pressure rose to 237 systolic and 143 mm. diastolic. The patient was discharged from the clinic and readmitted a month later. The blood pressure average was 224 mm. Hg systolic and 130 mm. diastolic. Kidney extract was administered and the blood pressure fell within


No. M.B.
Hosp. No. 764
♂
35 yrs.
ht. 5'6½" cm.
Weight 137 LB. kg.
MALIGNANT HYPERTENSION
MONTHS
1 15 52 54 55 56 57
BLOOD VESSELS
BLOOD PRESSURE
KE
FUNDUS CHANGES
Cer. art.
Sclr. art.
Exudate
Ret. hem.
Pap. Edem.
KIDNEYS
UREA CLEARANCE % average normal
NON-PROTEIN URINE - SPECIFIC GRAVITY
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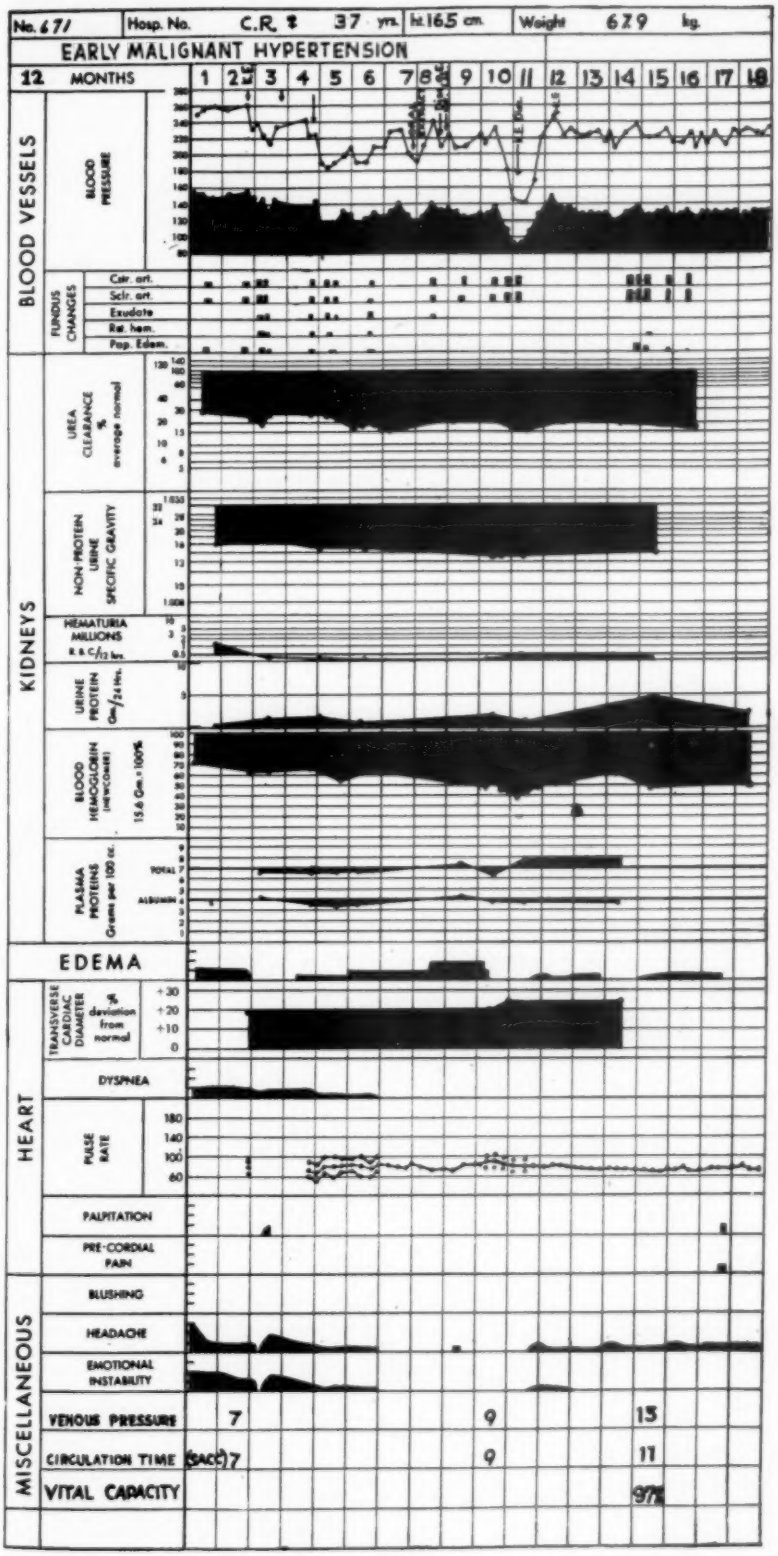
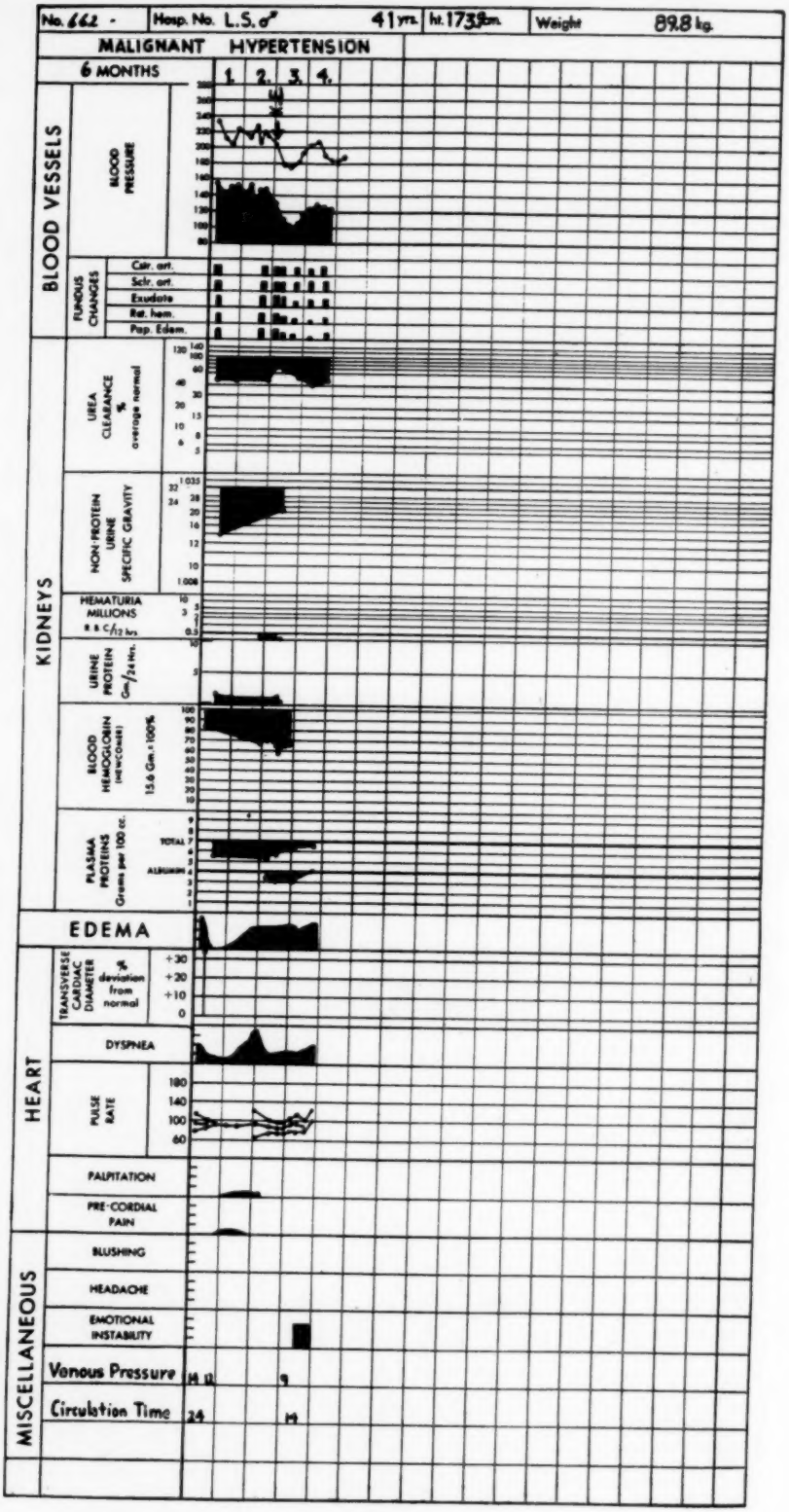
PLASMA PROTEINS Grams per 100 cc.
TOTAL
ALBUMIN
EDEMA
HEART
TRANSVERSE CARDIAC DIAMETER % deviation from normal
+30
+20
+10
0
DYSPNEA
PULSE RATE
180
140
100
60
PALPITATION
PRE-CORDIAL PAIN
MISCELLANEOUS
BLUSHING
HEADACHE
EMOTIONAL INSTABILITY
Venous Pressure cm. of Blood
Circulation Time Saccharin
Vital Capacity % of Normal


No. 671
Hosp. No.
C.R. ♀ 37 yrs.
ht. 165 cm.
Weight 67.9 kg.
EARLY MALIGNANT HYPERTENSION
12 MONTHS
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
BLOOD VESSELS
BLOOD PRESSURE
FUNDUS CHANGES
Cstr. art.
Sclr. art.
Exudate
Ret. hem.
Pap. Edem.
KIDNEYS
UREA CLEARANCE % average normal
NON PROTEIN URINE SPECIFIC GRAVITY
HEMATURIA MILLIONS R.B.C./c.mm.
URINE PROTEIN Gm./24 hrs.
BLOOD HEMOGLOBIN (HEWCOMER) 15.6 Gm. = 100%
PLASMA PROTEINS Grams per 100 cc.
TOTAL
ALBUMIN
EDEMA
HEART
TRANSVERSE CARDIAC DIAMETER % deviation from normal
DYSPNEA
PULSE RATE
PALPITATION
PRE-CORDIAL PAIN
MISCELLANEOUS
BLUSHING
HEADACHE
EMOTIONAL INSTABILITY
VENOUS PRESSURE
CIRCULATION TIME
VITAL CAPACITY
7
9
13
7
9
11
97%


No. 662 -
Hosp. No. L.S. ♂
41 yrs.
ht. 1738m.
Weight 89.8 kg.
MALIGNANT HYPERTENSION
6 MONTHS
1. 2. 3. 4.
BLOOD VESSELS
BLOOD PRESSURE
FUNDUS CHANGES
Calr. art.
Sclr. art.
Exudate
Ret. hem.
Pap. Edem.
KIDNEYS
UREA CLEARANCE % average normal
NON PROTEIN URINE SPECIFIC GRAVITY
HEMATURIA MILLIONS R.B.C/12 hrs.
URINE PROTEIN Gm/24 Hrs.
BLOOD HEMOGLOBIN (METYCOMB) 15.6 Gm. = 100%
PLASMA PROTEINS Grams per 100 cc.
TOTAL
ALBUMIN
EDEMA
HEART
TRANSVERSE CARDIAC DIAMETER % deviation from normal
+30
+20
+10
0
DYSPNEA
PULSE RATE
180
140
100
60
PALPITATION
PRE-CORDIAL PAIN
MISCELLANEOUS
BLUSHING
HEADACHE
EMOTIONAL INSTABILITY
Venous Pressure
Circulation Time
24

two days to an average of 195 mm. Hg systolic and 124 mm. diastolic and continued down to 185 mm. Hg systolic and 117 mm. diastolic.

Urea clearance was low (16 per cent) and did not change significantly during treatment. It is of interest that the T-waves which were inverted in Leads I and II became upright. Retinal hemorrhages, exudates, and papilledema disappeared.

After five months of treatment, dependent edema and headaches prompted readmission to the Lilly Clinic for intensive kidney extract therapy. During first week of treatment, blood pressure averaged 189 mm. Hg systolic and 115 mm. diastolic. She developed an abscess in her hip that was accompanied by a septic fever to 104° daily. Blood pressure fell to 126 mm. Hg systolic and 74 mm. diastolic. She complained of light headedness. Renal extract was discontinued and the lesion was incised and drained. The next three weekly blood pressure averages were 148 mm. Hg systolic and 92 mm. diastolic, 141 mm. systolic and 91 diastolic and 168 mm. systolic and 104 mm. diastolic. She was discharged to out-patient department. Without renal extract blood pressure rose to 246 mm. Hg systolic and 146 mm. diastolic. Extract treatment was started again and blood pressure has averaged 210 to 230 mm. Hg systolic and 120 to 130 mm. Hg diastolic. She has resumed her household duties and has only occasional headaches.

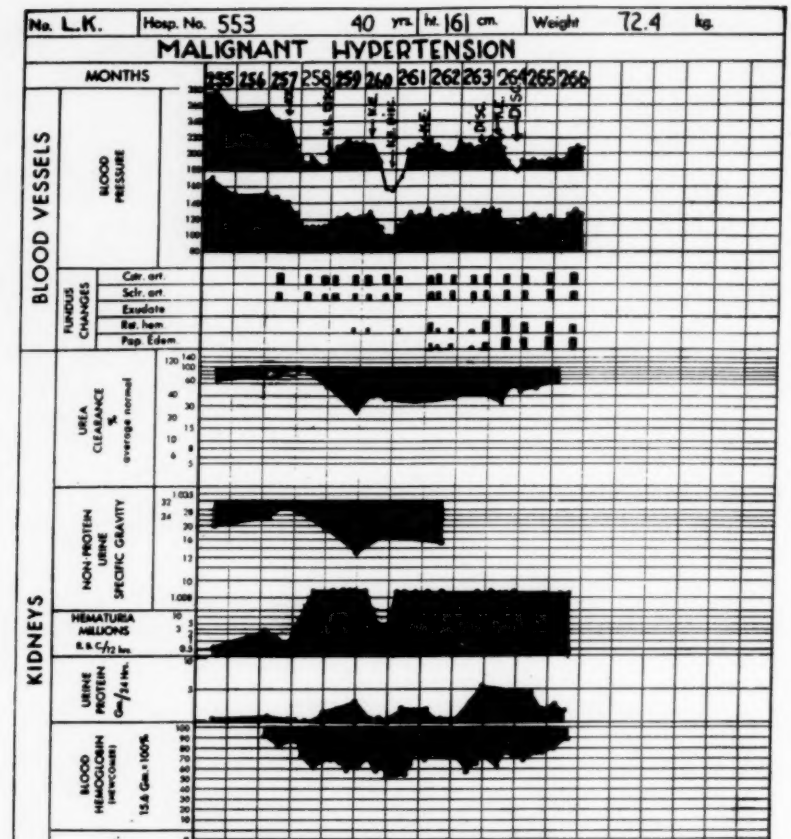
Case 5. L. S. (662). This 41-year-old man complained of dyspnea, headache, insomnia, nausea and vomiting, edema of the legs, and swelling of the abdomen. He knew that he had hypertension for four years, but two years before admission dyspnea and fatigability became pronounced. On admission he exhibited cyanosis of the extremities, orthopnea, grade 4 edema, and ascites. The eyegrounds showed grade 3 sclerosis and constriction of the vessels, grade 3 hemorrhages, exudates, and papilledema. The heart was markedly enlarged (+ 39 per cent deviation); the rate was rapid; and gallop rhythm was present. The venous pressure was elevated (12 cm. of blood), and many moist râles were heard in the chest. The electrocardiogram demonstrated numerous extrasystoles, depression of the S–T segment in Leads I, II, and III; inverted, splintered QRS in Lead III and biphasic QRS in Lead IV.

During the first four weeks after admission the blood pressure averaged 215 mm. Hg systolic and 150 mm. diastolic. The week following administration of kidney extract the pressure averaged 178 mm. Hg systolic and 110 mm. diastolic. He complained of less dyspnea, and the rhythm of the heart became regular. The papilledema receded. Extract was discontinued, and the blood pressure rose to near its former level; the pulse became irregular and rapid; and dyspnea returned. Urea clearance began to fall, and retinal hemorrhages appeared along with papilledema. A more purified but evidently weaker extract was again administered. The patient, however, became stuporous and complained of severe joint pains. Urea clearance continued to fall, and massive hemorrhages occurred from the bowel. The latter continued and apparently were the immediate cause of death. The diagnosis of malignant hypertension was confirmed at autopsy. The bleeding was coming from ulcers in the large bowel.

Case 6 (553). A white female, aged 38 years, complained of palpitation, headaches, insomnia, and precordial pain. Hypertension was discovered 21 years ago. In 1936, because of the severity of the hypertension, both splanchnic nerves were resected but within two weeks the pressure had risen to 190 mm. Hg systolic and 135 mm. diastolic. On admission to the Lilly Clinic in 1938 blood pressure was 248 mm. Hg systolic and 148 mm. diastolic. Maintenance doses of digitalis were being given before her admission because, on discontinuing it, decompensation occurred. Despite the long continued hypertension, the renal function was good.

Administration of thiocyanate for a period of 10 months brought no significant reduction of blood pressure.

Kidney extract administration was started six months ago. At first the extracts were not as potent as those now employed and the fall in blood pressure was cor-


No. L.K.
Hosp. No. 553
40 yrs.
ht. 161 cm.
Weight 72.4 kg.
MALIGNANT HYPERTENSION
MONTHS
255 256 257 258 259 260 261 262 263 264 265 266
BLOOD VESSELS
BLOOD PRESSURE
FUNDUS CHANGES
Cor. art
Sclr. art
Exudate
Ret. hem
Pap. Edem
KIDNEYS
UREA CLEARANCE % average normal
NON PROTEIN URINE SPECIFIC GRAVITY
HEMATURIA MILLIONS R.B.C./12 hr.
URINE PROTEIN Gm./24 hr.
BLOOD HEMOGLOBIN (HAWKSLEY) 15.6 Gm. = 100%
PLASMA PROTEINS Grams per 100 cc.
TOTAL
ALBUMIN
EDEMA
HEART
TRANSVERSE CARDIAC DIAMETER % deviation from normal
+30
+20
+10
0
DYSPNEA
PULSE RATE
180
140
100
60
PALPITATION
PRE-CORDIAL PAIN
MISCELLANEOUS
BLUSHING
HEADACHE
EMOTIONAL INSTABILITY
Venous Pressure cm. of Blood
Circulation Time Saccharin
Vital Capacity % of Normal

respondingly smaller. The average blood pressure over several years before administration of extract was 230 mm. Hg systolic and 134 mm. diastolic and after extract it had fallen to 172 mm. systolic and 104 mm. diastolic.

Because of inflammatory and fibrotic changes in the hips at the sites of earlier crude renal extract injections, therapy was discontinued and started again on several occasions. The rise and fall in blood pressure averages are noted on the graphic chart. Six months ago papilledema and retinal hemorrhages appeared in the ocular fundi, accompanied by gross hematuria, indicating onset of malignant hypertension. Eye ground changes were reversed and hematuria was reduced following kidney extract administration and reduction of the arterial pressure to averages of 155 mm. Hg systolic and 94 mm. diastolic. Again the damaged tissues of patient's buttocks necessitated termination of treatment. Rectal administration of renal extract failed to maintain desired blood pressure levels. Hemorrhages and papilledema again occurred in the eyegrounds. Cardiac decompensation has resumed and it was deemed unwise to continue extract treatment because of the many complications.

Case 7. This white male, aged 34, complained of headaches, and failing vision of about 18 months' duration. Vision became suddenly diminished. The headaches became so severe that it was necessary to give large amounts of codeine.

The patient appeared very ill. He was unable to read. Examination of the eyegrounds showed grade 3 constriction and sclerosis of the arterioles, grade 3 papilledema and exudates, and grade 2 hemorrhages. The heart was slightly enlarged (+ 14 per cent deviation). The S–T segments in Leads I, II, and III were depressed and the QRS complex was splintered in Lead III.

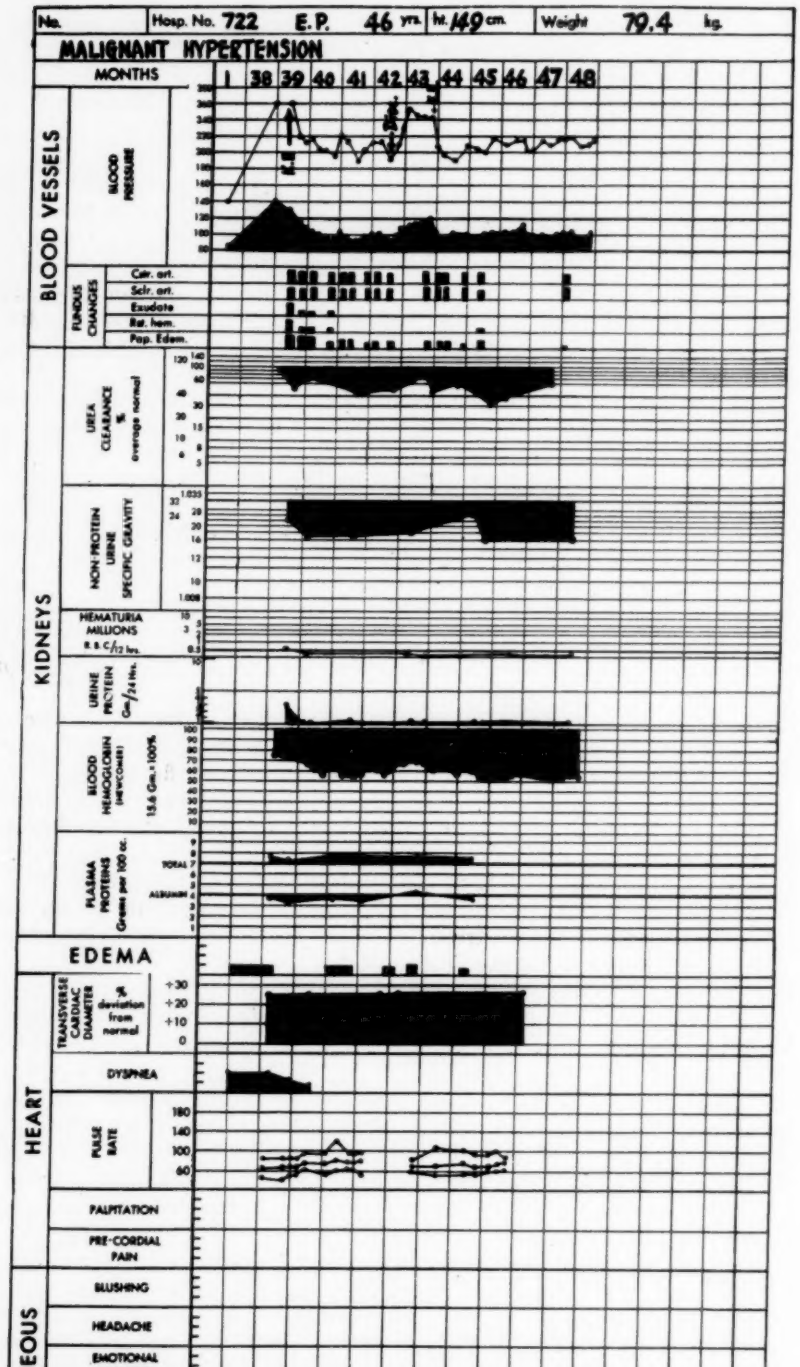
Shortly after admission the patient had a series of four convulsions. The arterial blood pressure was 278 mm. Hg systolic and 170 mm. diastolic and spinal fluid pressure 200 mm. of water. Severe vomiting then began, and all fluids had to be given by rectum. The patient became irrational. Since the outlook seemed so poor, kidney extract was administered. The blood pressure fell progressively. Without extract the diastolic pressure was seldom below 158 mm. Hg and often much higher; while with it, it was seldom above 130 mm. Hg. Hemorrhages disappeared from his eyegrounds, and the papilledema regressed so that he was able to read. Urea clearance was 13 per cent of normal when treatment was started and did not appear affected by it. Headaches were much reduced in severity.

Since we did not believe that the extremely low renal function was reversible, we could not conscientiously advise him to continue treatment. When it was discontinued and the patient allowed to go home, the blood pressure rose sharply, and he died within two weeks.

Case 8. E. P. (722). This 46-year-old colored patient noticed that two years ago she became short of breath on slight exertion, and one year ago swelling of her feet and ankles occurred. Exertion brought on attacks of a smothering feeling in her chest and severe palpitation. Ten days before admission mild apoplexy occurred followed by moderate left hemiplegia. Nocturia became persistent. Anginal pains also occurred on even slight exertion.

The patient is obese. Eyegrounds showed grade 3 constriction, sclerosis, exudates, papilledema, and hemorrhages, both fresh and old. Blood pressure on admission was 310 mm. Hg systolic and 124 mm. diastolic. The heart was enlarged (27 + per cent deviation). The T-waves in Leads I, II, III, and IV were inverted; the P-wave in Lead III isoelectric. Urea clearance was 70 per cent of normal. Vital capacity was reduced to 40 per cent of normal. Retrograde pyelograms show that there was bilateral hydronephrosis, but cultures of the urine were negative.

Kidney extract was administered after the blood pressure had been stabilized at an average level of 260 mm. Hg systolic and 136 mm. diastolic. During the next week it had fallen to an average of 216 mm. Hg systolic and 103 mm. diastolic; the


No.
Hosp. No. 722
E. P.
46 yrs.
ht. 149 cm.
Weight 79.4 kg.
MALIGNANT HYPERTENSION
MONTHS
1 38 39 40 41 42 43 44 45 46 47 48
BLOOD VESSELS
BLOOD PRESSURE
FUNDUS CHANGES
Cer. art.
Sclr. art.
Exudate
Ret. hem.
Pap. Edem.
KIDNEYS
UREA CLEARANCE % average normal
NON-PROTEIN URINE SPECIFIC GRAVITY
HEMATURIA MILLIONS R. B. C./12 hrs.
URINE PROTEIN Gm./24 Hrs.
BLOOD HEMOGLOBIN (HAWKSLEY) 13.6 Gm. = 100%
PLASMA PROTEINS Grams per 100 cc.
TOTAL
ALBUMIN
EDEMA
HEART
TRANSVERSE CARDIAC DIAMETER % deviation from normal
+30
+20
+10
0
DYSPNEA
PULSE RATE
180
140
100
60
PALPITATION
PRE-CORDIAL PAIN
MISCELLANEOUS
BLUSHING
HEADACHE
EMOTIONAL INSTABILITY
Venous Pressure cm. of Blood
Circulation Time Saccharin
Vital Capacity % of Normal

second week 205 mm. Hg systolic and 100 mm. diastolic; the third week 202 mm. Hg systolic and 100 mm. diastolic; and the fourth week 202 mm. Hg systolic and 97 mm. diastolic. Marked regression of the eyeground changes occurred. There was less exudate and only a small amount of hemorrhage. Proteinuria diminished from 3 gm. in 24 hours to less than 0.1 gm. Hemoglobin was not changed significantly (70 per cent). The electrocardiogram, taken three weeks after treatment was initiated, showed inversion of the T-waves in Leads I, II, and III but not in Lead IV.

After two months of kidney extract the weekly arterial blood pressure average was 191 mm. Hg systolic and 88 mm. diastolic. The patient had no complaints. The optic fundi revealed grade 3 constriction and sclerosis of retinal arterioles with grade 2 papilledema and no hemorrhages or exudates. Kidney extract was discontinued, and arterial blood pressure average for the first week was 252 mm. Hg systolic and 110 mm. diastolic; second week 230 mm. Hg systolic and 107 mm. diastolic; and third week 246 mm. Hg systolic and 115 mm. diastolic. Kidney extract therapy was resumed; the arterial blood pressure average for the week was 209 mm. Hg systolic and 99 mm. diastolic; the second week was 196 mm. Hg systolic and 94 mm. diastolic.

After approximately eight months of kidney extract therapy patient has no complaints and leads a rather quiet home life. Weekly arterial blood pressure averages vary from 203 to 219 mm. Hg systolic and 97 to 104 mm. Hg diastolic. T-waves are inverted in Leads I, II, and IV; they are biphasic in Lead III. There are no hemorrhages or exudates present in optic fundi, and papilledema is grade 2. Urine protein equals 0.3 gm. per 24 hours, and hemoglobin is 66 per cent.

Approximately 12 shock-like reactions have occurred and occasional episodes of pain in back and chest have been experienced during the course of treatment.

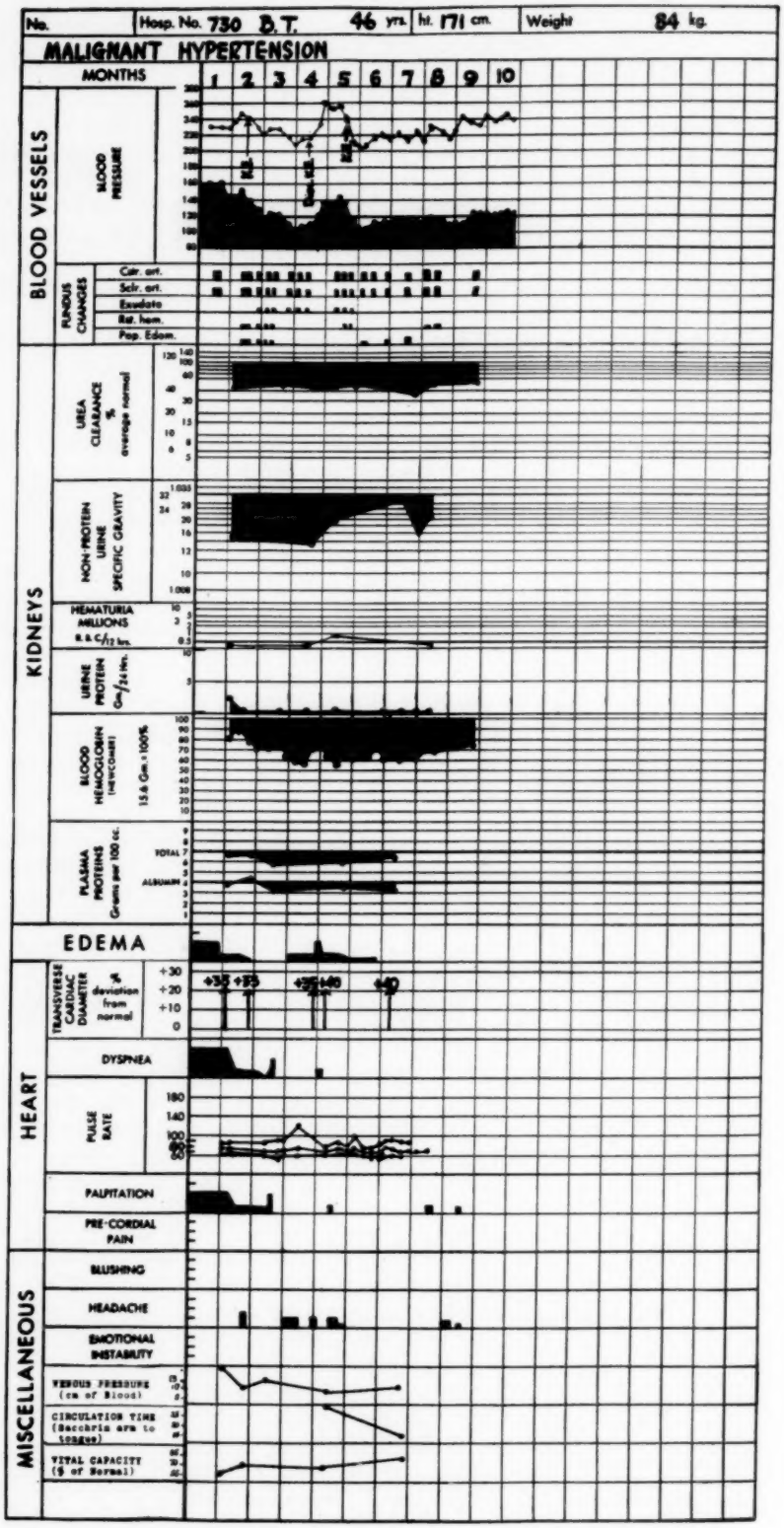
Case 9. B. T. (730). This colored female, 46 years of age, discovered she had hypertension in 1938. Her complaints on admission were nocturia of many years' duration, headaches, fatigability, progressive loss of memory and eyesight, ringing in her ears, and on two occasions severe epistaxis.

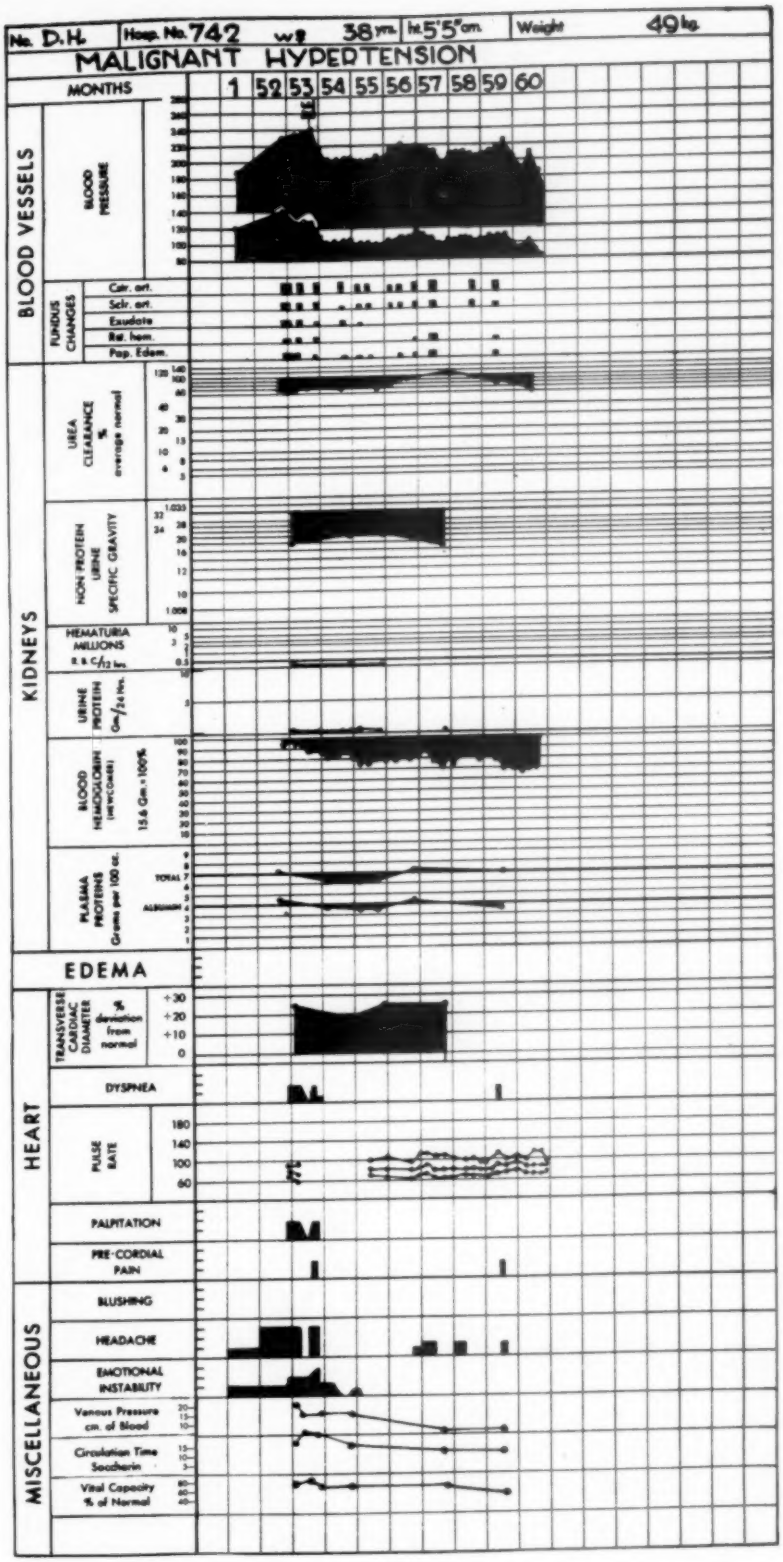
On examination there were seen in the optic fundi grade 3 constriction and sclerosis of the retinal arterioles, grade 1 hemorrhages, and grade 1 papilledema. The heart was greatly enlarged, the mediastinum was widened, and a systolic murmur was heard at the cardiac apex and at the left sternal border in the second interspace. The liver was palpable 2.5 cm. below the right costal margin. During the control period of observation she became decompensated and was digitalized.

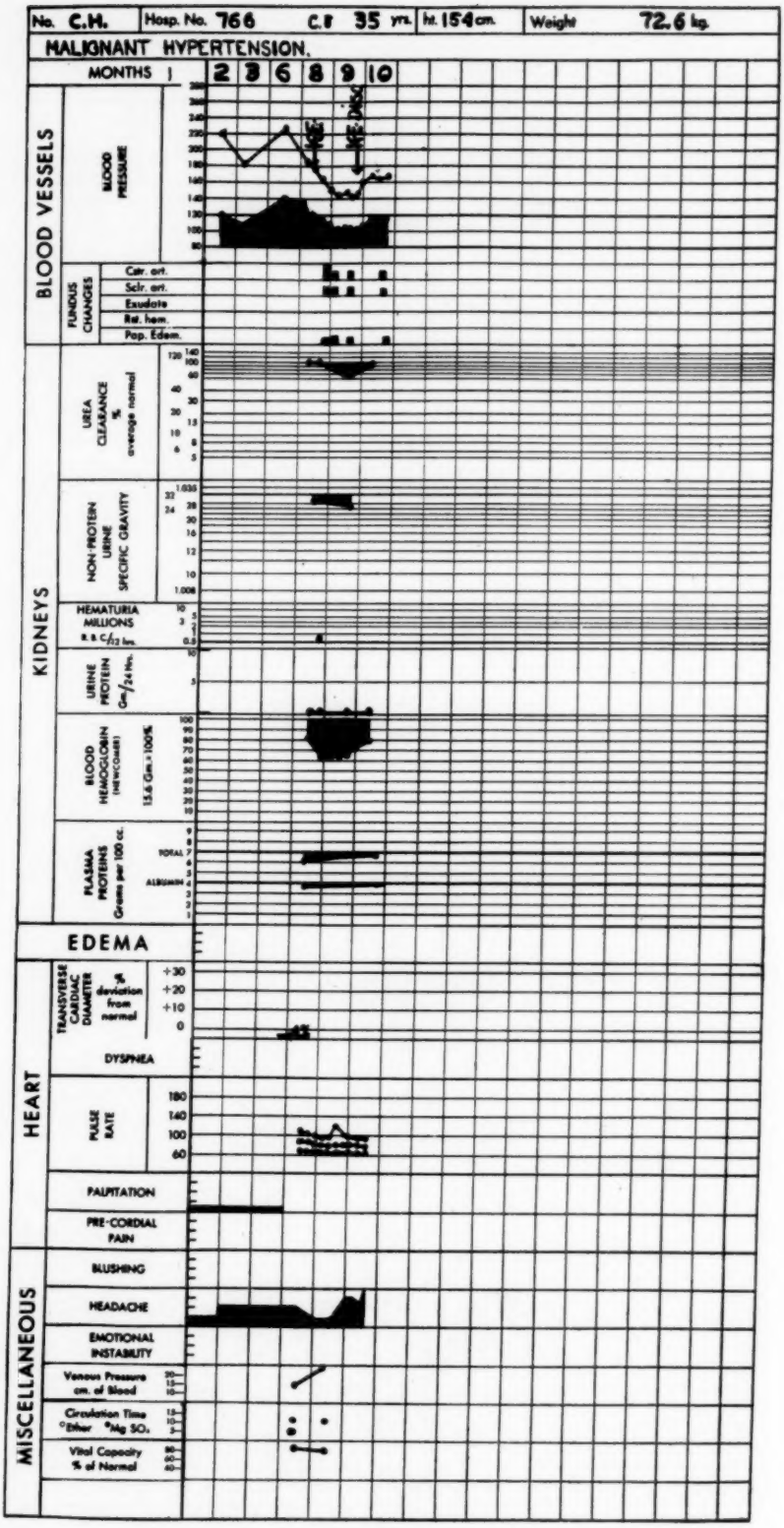
Urea clearance was 42.7 per cent of average normal. Addis examination revealed a maximum specific gravity of 1.015. Transverse cardiac diameter was + 35 per cent of normal. The electrocardiogram showed inverted T-waves in Leads I and IV and biphasic T-waves in Lead II. Blood Kline was 2+ and Kahn was 3+. Arterial blood pressure average was 241 mm. Hg systolic and 130 mm. diastolic for a week before kidney extract therapy was instituted. The arterial blood pressure average fell gradually to 209 mm. Hg systolic and 106 mm. diastolic. Kidney extract was discontinued for three weeks and the blood pressure rose to an average of 253 mm. Hg systolic and 136 mm. diastolic. Symptoms of mild decompensation appeared and headaches returned. Kidney extract therapy was resumed, and arterial blood pressure fell within two weeks to average 204 mm. Hg systolic and 106 mm. diastolic.

The patient was discharged from the hospital, is symptom free, and has resumed her household duties. Weekly arterial blood pressure averages vary from 224 to 243 mm. Hg systolic and 113 to 130 mm. Hg diastolic. The electrocardiogram now exhibits biphasic T-waves in Leads I and III and inverted T-waves in Leads II and IV. The optic fundi show grade 3 constriction and sclerosis of retinal arterioles, no hemorrhages, and a ± papilledema. Urea clearance is 46.5 per cent average normal. Maximum urinary specific gravity is 1.016.

The patient has had three shock-like reactions and many episodes of cramping pain in chest and back following injections of kidney extract.


No.
Hosp. No. 730 B.T. 46 yrs.
ht. 171 cm.
Weight 84 kg.
MALIGNANT HYPERTENSION
MONTHS
1 2 3 4 5 6 7 8 9 10
BLOOD VESSELS
BLOOD PRESSURE
FUNDUS CHANGES
Cer. art.
Sclr. art.
Exudate
Ret. hem.
Pap. Edem.
KIDNEYS
UREA CLEARANCE % average normal
NON-PROTEIN URINE SPECIFIC GRAVITY
HEMATURIA MILLIONS
R & C/12 hrs.
URINE PROTEIN Gm/24 Hrs.
BLOOD HEMOGLOBIN (HEVCOMB) 15.6 Gm. = 100%
PLASMA PROTEINS Grams per 100 cc.
TOTAL
ALBUMIN
EDEMA
HEART
TRANSVERSE CARDIAC DIAMETER % deviation from normal
+30
+20
+10
0
+35 +55 +35+45 +40
DYSPNEA
PULSE RATE
PALPITATION
PRE-CORDIAL PAIN
MISCELLANEOUS
BLUSHING
HEADACHE
EMOTIONAL INSTABILITY
VENOUS PRESSURE (cm of Blood)
CIRCULATION TIME (Saccharin arm to tongue)
VITAL CAPACITY (% of Normal)


No. D.H.
Hosp. No. 742
w.g.
38 yrs.
ht. 5'5" cm.
Weight
49 kg.
MALIGNANT HYPERTENSION
MONTHS
1 52 53 54 55 56 57 58 59 60
BLOOD VESSELS
BLOOD PRESSURE
FUNDUS CHANGES
Cor. art.
Sclr. art.
Exudate
Ret. hem.
Pap. Edem.
KIDNEYS
UREA CLEARANCE % average normal
NON-PROTEIN URINE SPECIFIC GRAVITY
HEMATURIA MILLIONS R.B.C./12 hrs.
URINE PROTEIN Gm./24 hrs.
BLOOD HEMOGLOBIN (NEWCOMER) 15.6 Gm. = 100%
PLASMA PROTEINS Grams per 100 cc.
TOTAL
ALBUMIN
EDEMA
HEART
TRANSVERSE CARDIAC DIAMETER % deviation from normal
+30
+20
+10
0
DYSPNEA
PULSE RATE
180
140
100
60
PALPITATION
PRE-CORDIAL PAIN
MISCELLANEOUS
BLUSHING
HEADACHE
EMOTIONAL INSTABILITY
Venous Pressure cm. of Blood
Circulation Time Saccharin
Vital Capacity % of Normal


No. C.H.
Hosp. No. 766
C.I 35 yrs.
ht. 154 cm.
Weight 72.6 kg.
MALIGNANT HYPERTENSION.
MONTHS 1 2 3 6 8 9 10
BLOOD VESSELS
BLOOD PRESSURE
FUNDUS CHANGES
Cstr. art.
Sclr. art.
Exudate
Ret. hem.
Pap. Edem.
KIDNEYS
UREA CLEARANCE % average normal
NON-PROTEIN URINE SPECIFIC GRAVITY
HEMATURIA MILLIONS R. B. C/12 hrs.
URINE PROTEIN Gm/24 Hrs.
BLOOD HEMOGLOBIN (NEWCOMER) 15.6 Gm = 100%
PLASMA PROTEINS Grams per 100 cc.
TOTAL
ALBUMIN
EDEMA
HEART
TRANSVERSE CARDIAC DIAMETER % deviation from normal
DYSPNEA
PULSE RATE
PALPITATION
PRE-CORDIAL PAIN
MISCELLANEOUS
BLUSHING
HEADACHE
EMOTIONAL INSTABILITY
Venous Pressure cm. of Blood
Circulation Time °Ether °Mg SO4
Vital Capacity % of Normal

Case 10. D. H. (742). A white female, 38 years of age, complained of hypertension known for five years, fatigability, palpitation, dyspnea, and excessive perspiration. Six months before admission she had two attacks of paroxysmal nocturnal dyspnea, disabling headaches with nausea and vomiting. Blood pressure was 232 mm. Hg systolic and 130 mm. diastolic. Ocular fundi revealed grade 2 constriction and grade 3 sclerosis of the retinal vessels, grade 1 papilledema and hemorrhages. The heart was enlarged in all diameters, especially to the left (+25 deviation). The second heart sound was reduplicated in all areas. There were râles at both lung bases. The liver edge was palpated 1½ cm. below the right costal margin.

Urea clearance was 70 per cent of average normal; maximal ability to concentrate urine was 1.018. Venous pressure was 22 cm. of blood and circulation time 20 seconds (saccharin arm to tongue). Vital capacity was 80 per cent of average normal. The electrocardiogram showed left axis deviation and T-waves inverted in Leads I and II.

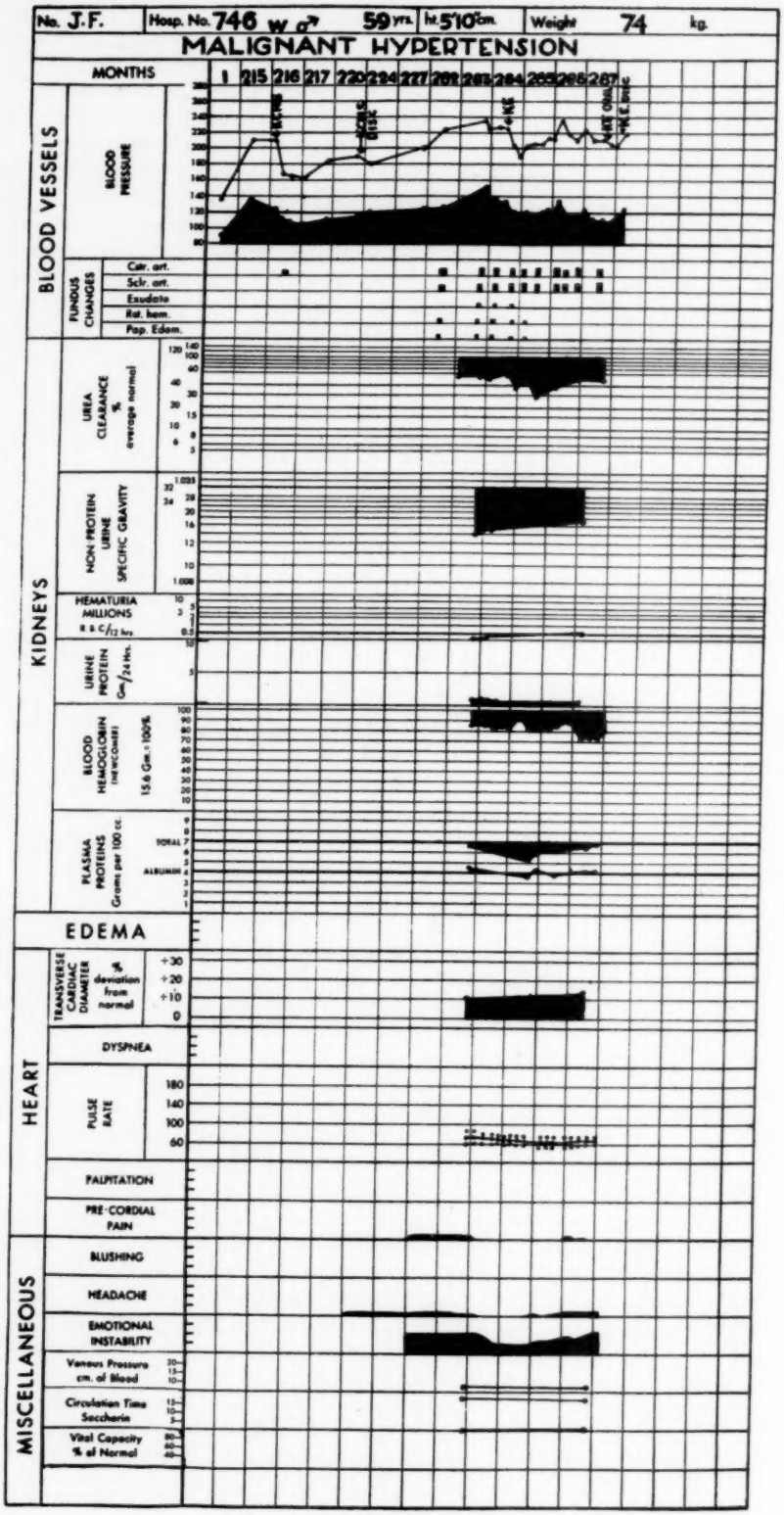
This patient was digitalized and kept at bed rest for three weeks. Arterial pressure averaged 238 mm. Hg systolic and 128 mm. diastolic. Symptoms of decompensation disappeared. Venous pressure fell to 15 cm. of blood, and circulation time to 15 seconds. Kidney extract was begun at the end of the third week during bed rest. Arterial pressure fell to an average of 205 mm. Hg systolic and 104 mm. diastolic. Venous pressure became 7 cm. of blood. Circulation time was 12 seconds. The hypertensive retinopathy improved to leave only grade 3 constriction and grade 2 sclerosis of the retinal vessels. All subjective symptoms disappeared.

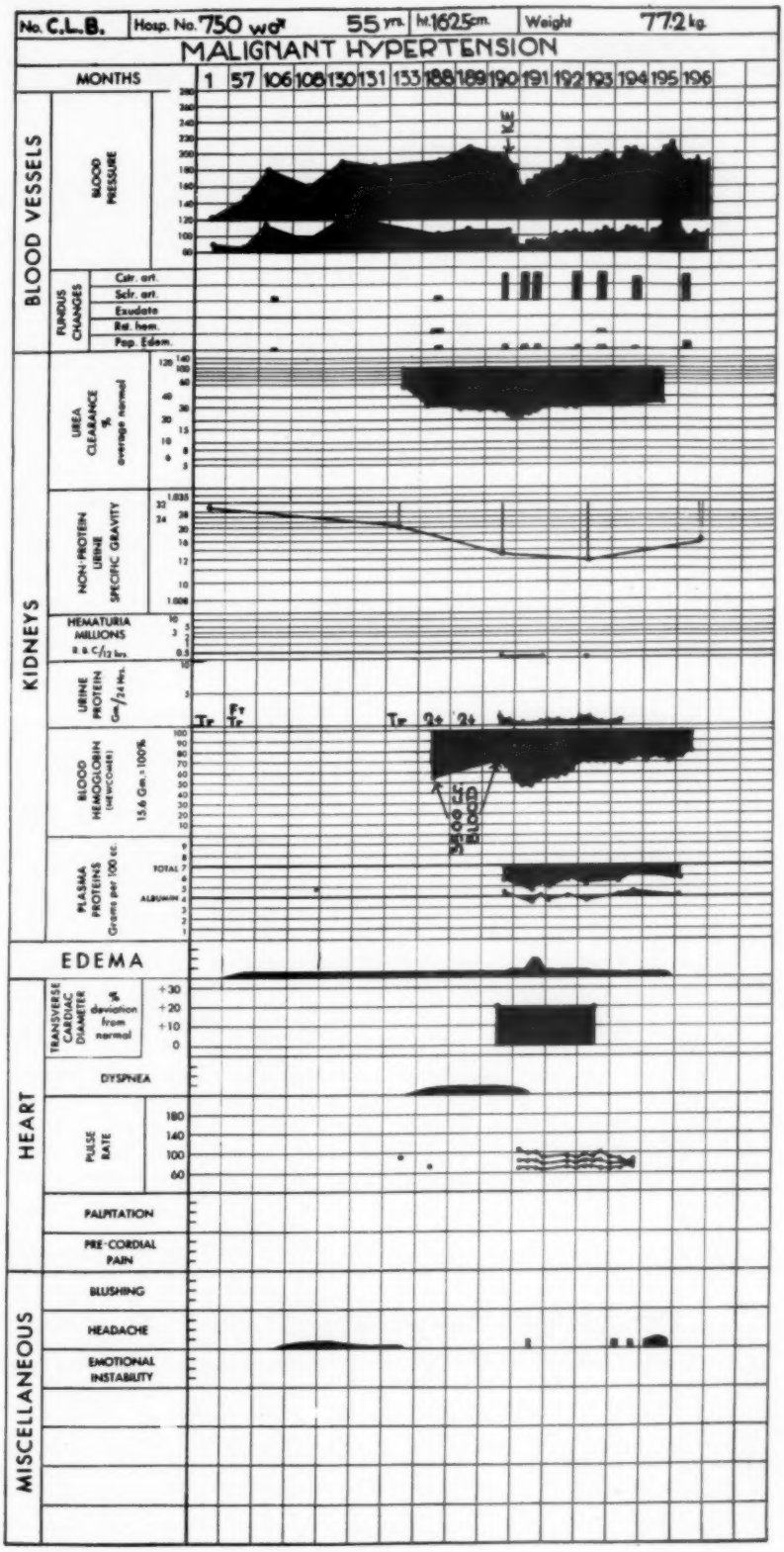
Treatment extended over six months' time. She had chills and fever with urticaria on an average of once weekly, and two shock-like reactions. During the sixth month of treatment with intramuscular kidney extract she complained of joint pains. These followed kidney extract injections. Eosinophilia (8 per cent) was found and the skin was sensitive to 1:1,000 dilution of kidney extract. When kidney extract and digitalis were discontinued six days the blood pressure rose to a weekly average of 224 mm. Hg systolic and 112 mm. diastolic, and during one period of three days it reached 260 mm. Hg systolic and 120 mm. diastolic. Acute left ventricular failure supervened. Two small hemorrhages and grade 1 papilledema were seen in ocular fundi. Restoration of cardiac compensation, administration of kidney extract following rapid desensitization reduced the blood pressure to an average of 200 mm. Hg systolic and 98 mm. diastolic with only partial relief of joint pains. Abdominal pain replaced the joint pains, and was of such severity as to suggest intestinal obstruction. After partial decompression, tenderness localized over the right upper quadrant. An exploratory operation revealed that the gall-bladder was edematous and thickened. A number of enlarged lymph nodes was seen, and nodules were felt in the liver. Microscopic examination showed a quite typical picture of periarteritis nodosa.

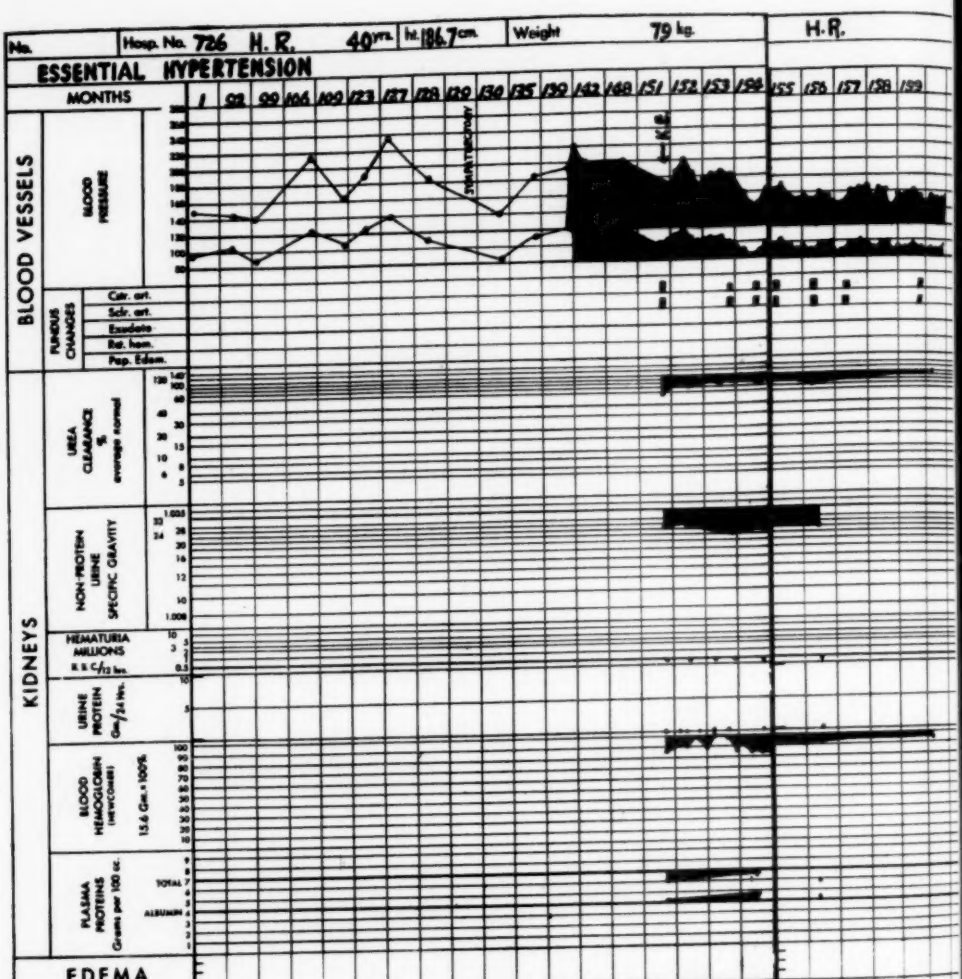
Case 11. C. H. (766). A colored female, aged 35, complained of headaches and dizziness for eight months, hypertension known for six months, and blindness.

Average arterial blood pressure was 186 mm. Hg systolic and 136 mm. diastolic. Examination of the ocular fundi showed grade 4 constriction of the retinal arterioles, and grade 3 sclerosis. Both nerve heads were irregular in outline, swollen and paler than normal. The electrocardiogram displayed left axis deviation. Urea clearance was 100 per cent of average normal. Maximal ability to concentrate urine was 1.030.

The first weekly average arterial blood pressure at bed rest was 186 mm. Hg systolic and 136 mm. diastolic. Renal extract was administered intramuscularly. The blood pressure fell to an average level of 142 mm. Hg systolic and 103 mm. diastolic for four weeks. Headaches were diminished in severity but sight was not restored. Constriction of retinal arterioles was reduced to grade 2. Kidney extract was discontinued. The arterial blood pressure rose to average 168 mm. Hg systolic and 118 mm. diastolic in two weeks' time and headaches recurred.


No. J.F.
Hosp. No. 746 W ♂ 59 yrs.
Ht. 5'10" cm.
Weight 74 kg.
MALIGNANT HYPERTENSION
MONTHS
1 215 216 217 220 224 227 281 283 284 285 286 287
BLOOD VESSELS
BLOOD PRESSURE
FUNDUS CHANGES
Constr. art.
Sclr. art.
Exudate
Ret. hem.
Pap. Edem.
KIDNEYS
UREA CLEARANCE % average normal
NON-PROTEIN URINE SPECIFIC GRAVITY
HEMATURIA MILLIONS R B C/12 hrs.
URINE PROTEIN Gm/24 Hrs.
BLOOD HEMOGLOBIN (HAEMOGLOBIN) 15.6 Gm. = 100%
PLASMA PROTEINS Grams per 100 cc.
TOTAL
ALBUMIN
EDEMA
HEART
TRANSVERSE CARDIAC DIAMETER % deviation from normal
DYSPNEA
PULSE RATE
PALPITATION
PRE-CORDIAL PAIN
MISCELLANEOUS
BLUSHING
HEADACHE
EMOTIONAL INSTABILITY
Venous Pressure cm. of Blood
Circulation Time Saccharin
Vital Capacity % of Normal


No. C.L.B.
Hosp. No. 750 wo♂
55 yrs.
ht. 1625 cm.
Weight 77.2 kg.
MALIGNANT HYPERTENSION
MONTHS
1 57 106 108 130 131 133 188 189 190 191 192 193 194 195 196
BLOOD VESSELS
BLOOD PRESSURE
FUNDUS CHANGES
Calc. art.
Sclr. art.
Exudate
Ret. hem.
Pap. Edem.
KIDNEYS
UREA CLEARANCE % average normal
NON-PROTEIN UREINE SPECIFIC GRAVITY
HEMATURIA MILLIONS R. B. C/12 hrs.
URINE PROTEIN Gm/24 Hrs.
BLOOD HEMOGLOBIN (Haven-Gault) 13.6 Gm. = 100%
PLASMA PROTEINS Grams per 100 cc.
TOTAL
ALBUMIN
EDEMA
HEART
TRANSVERSE CARDIAC DIAMETER % deviation from normal
DYSPNEA
PULSE RATE
PALPITATION
PRE-CORDIAL PAIN
MISCELLANEOUS
BLUSHING
HEADACHE
EMOTIONAL INSTABILITY
Tr
Ft
Tr
Tr
24
24
Saline to Blood


No.
Hosp. No. 726 H. R. 40yrs. ht. 186.7cm. Weight 79 kg.
H.R.
ESSENTIAL HYPERTENSION
MONTHS
1 92 99 106 109 123 127 128 129 130 135 139 142 148 151 152 153 154 155 156 157 158 159
STRATTON DAY
K.P.
BLOOD VESSELS
BLOOD PRESSURE
FUNDUS CHANGES
Cor. art.
Sclr. art.
Exudate
Ret. hem.
Pap. Edem.
KIDNEYS
UREA CLEARANCE % average normal
NON-PROTEIN URINE SPECIFIC GRAVITY
HEMATURIA MILLIONS R. B. C/12 hr.
URINE PROTEIN Gm/24 hrs.
BLOOD HEMOGLOBIN (NEWCOMER) 13.6 Gm.=100%
PLASMA PROTEINS Grams per 100 cc.
TOTAL
ALBUMIN
EDEMA
HEART
TRANSVERSE CARDIAC DIAMETER % deviation from normal
+30
+20
+10
0
DYSPNEA
PULSE RATE
180
140
100
60
PALPITATION
PRE-CORDIAL PAIN
MISCELLANEOUS
BLUSHING
HEADACHE
EMOTIONAL INSTABILITY
Venous Pressure cm. of Blood
Circulation Time Saccharin
Vital Capacity % of Normal

Case 12. J. F. (746). This white male, aged 59 years, had hypertension of eight years' duration (190 to 270 mm. Hg systolic and 100 to 170 mm. Hg diastolic). Potassium thiocyanate was given in 1935 and the arterial pressure was reduced to an average of 164 mm. Hg systolic and 100 mm. diastolic. The symptoms on admission were convulsive seizures with loss of consciousness, impaired memory and reasoning power. The blood pressure was 236 mm. Hg systolic and 150 mm. diastolic. The ocular fundi disclosed grade 3 constriction and sclerosis of retinal vessels, grade 1 hemorrhages, exudates, and papilledema. The heart was enlarged to left, 11 cm. from midline. There were frequent extrasystoles. A marked tremor in the outstretched hands was observed. Urea clearance was 55 per cent of average normal. Maximal ability to concentrate urine was 1.015. Proteinuria amounted to 1 gm. daily. The electrocardiogram exhibited left axis deviation and inverted T-waves in Lead I.

During bed rest the blood pressure averaged 225 mm. Hg systolic and 136 mm. diastolic. Kidney extract was administered intramuscularly; the arterial pressure averaged 202 mm. Hg systolic and 134 mm. diastolic for first week of treatment and 192 mm. Hg systolic and 120 mm. diastolic for second week. For three months of treatment arterial pressure averaged 210 mm. Hg systolic and 118 mm. diastolic.

This course of therapy was attended with one shock-like reaction and six reactions with back and chest pain, chills, and fever. The mental state cleared. Retinal hemorrhages and exudates absorbed; papilledema regressed. The T-waves in Lead I of the electrocardiogram became upright.

Essential Hypertension

Case 13. C. B. (750). This 55-year-old white male complained of hypertension known for 20 years; headaches for five years that were relieved by bed rest and potassium thiocyanate; dependent edema of five years' duration; increasing nocturia; easy fatigability. His blood hemoglobin was maintained at 65 to 70 per cent of average normal by virtue of seven 500 c.c. blood transfusions in a period of two months.

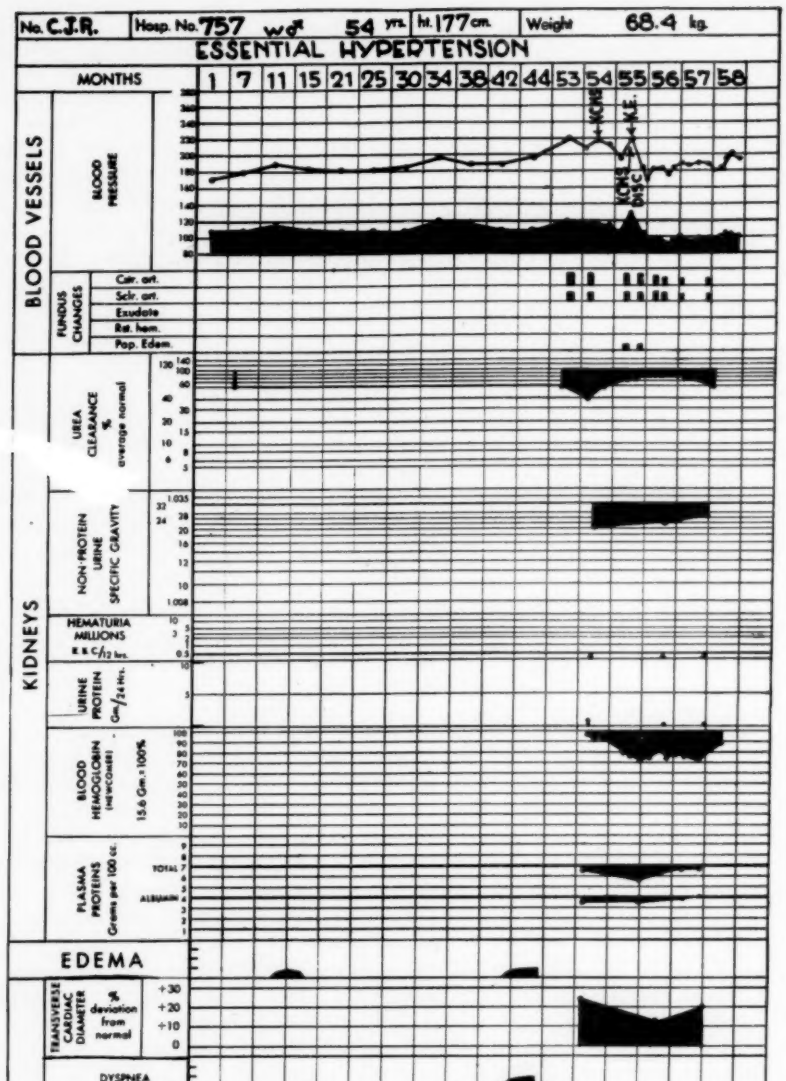
Physical findings were: arterial pressure of 210 mm. Hg systolic and 114 mm. diastolic; grade 3 constriction and grade 4 sclerosis of the retinal arterioles; the heart was slightly enlarged in all diameters; there was grade 1 pitting edema of the lower extremities.

Urea clearance was 28.4 per cent of average normal; maximal ability to concentrate urine was 1.0135; proteinuria amounted to 1.6 gm. per 24 hours; plasma proteins were 5.74 gm. per 100 c.c.

'Reticulogen' (Parenteral Liver Extract with Vitamin B_1, Lilly), ferrous sulfate, and daily doses of 'Multicebrin' failed to give a reticulocyte response or rise in blood hemoglobin. Hemoglobin reached a low of 46 per cent of average normal without transfusions. The blood pressure average for the first week in the hospital was 197 mm. Hg systolic and 110 mm. diastolic. Kidney extract was administered intramuscularly. After one week of therapy the blood pressure averaged 157 mm. Hg systolic and 84 mm. diastolic. This low level was maintained for only four weeks. During the following four months the pressure gradually rose to 190 to 200 mm. Hg systolic and 95 to 105 mm. Hg diastolic. Blood hemoglobin rose without transfusion to an average of 77 per cent of normal. Plasma proteins rose to 6.2 gm. per 100 c.c. All symptoms, including dependent edema, have disappeared.

This patient averaged a weekly bout of back and chest pain with chills and fever.

Case 14. H. R. (726). A 40-year-old white male was observed to have hypertension in a routine physical examination four years ago. He had had headaches for eight years; disabling anginal pain and dyspnea. Rest and sedation, potassium thiocyanate, and bilateral splanchnic nerve resection gave no relief of symptoms or permanent fall in arterial blood pressure. He came to Lilly Clinic in an ambulance after three months in bed.


No. C.J.R.
Hosp. No. 757
wd
54 yrs.
ht. 177 cm.
Weight 68.4 kg.
ESSENTIAL HYPERTENSION
MONTHS
1 7 11 15 21 25 30 34 38 42 44 53 54 55 56 57 58
KCNS
K.E.
KCNS DISC'D
BLOOD VESSELS
BLOOD PRESSURE
FUNDUS CHANGES
Cer. art.
Sclr. art.
Exudate
Ret. hem.
Pap. Edem
KIDNEYS
UREA CLEARANCE % average normal
NON-PROTEIN URINE SPECIFIC GRAVITY
HEMATURIA MILLIONS R.B.C./12 hrs.
URINE PROTEIN Gm./24 Hrs.
BLOOD HEMOGLOBIN (Haworth) 15.6 Gm. = 100%
PLASMA PROTEINS Grams per 100 cc.
TOTAL
ALBUMIN
EDEMA
HEART
TRANSVERSE CARDIAC DIAMETER % deviation from normal
DYSPNEA
PULSE RATE
PALPITATION
PRE-CORDIAL PAIN
MISCELLANEOUS
BLUSHING
HEADACHE
EMOTIONAL INSTABILITY
Venous Pressure cm. of Blood
Circulation Time °Ether °Mg SO4
Vital Capacity % of Normal
KCNS Level mg./100 cc.
KCNS Dose Gm./Day

Blood pressure ranged from 170 to 205 mm. Hg systolic and 110 to 120 diastolic. Ocular fundi revealed grade 2 constriction and grade 1 sclerosis of the retinal vessels. Heart was enlarged to 10.5 cm. to left of midline. Urea clearance was 85 per cent of average normal; maximal ability to concentrate urine was 1.024. Electrocardiogram revealed left axis deviation.

Kidney extract given intramuscularly daily failed to lower blood pressure appreciably for seven weeks. At the end of this time, it began to fall and has been maintained at 140 to 158 mm. Hg systolic and 80 to 98 mm. Hg diastolic for six months. He has been treated as an out-patient for five months, leads a normal life, and is relatively free of symptoms.

He has had two shock-like reactions and four bouts of pain with chill and fever in seven months' time.

Case 15. C. R. (757). This 54-year-old white male was found five years ago to have hypertension (172 mm. Hg systolic and 110 mm. diastolic) by an insurance physician. His complaints have been: increasing fatigue, headaches, extreme irritability, and personality change. He was treated with rest, potassium iodide, and sodium nitrite with no reduction in arterial pressure. He was treated intensively with potassium thiocyanate with no improvement.

Blood pressure averaged 220 mm. Hg systolic and 120 mm. diastolic. Arterioles in the ocular fundi showed grade 3 constriction, grade 2 sclerosis, and reddening of the optic discs. Chest film revealed cardiac hypertrophy to + 25 per cent of average normal. Urea clearance was 80 per cent of average normal. Maximal ability to concentrate urine was 1.022. The electrocardiogram exhibited inverted T-waves in Leads I, II, and IV and left axis deviation.

At bed rest under potassium thiocyanate the blood pressure averaged 216 mm. Hg systolic and 118 mm. diastolic. Potassium thiocyanate was discontinued and after a suitable period kidney extract was administered intramuscularly; the blood pressure fell to an average of 172 mm. Hg systolic and 96 mm. diastolic during first week of treatment. It has remained between 170 to 190 systolic and 92 to 100 diastolic during three months of treatment. Constriction of retinal arterioles was reduced to grade 2. The symptoms have disappeared, and his former genial personality has returned.

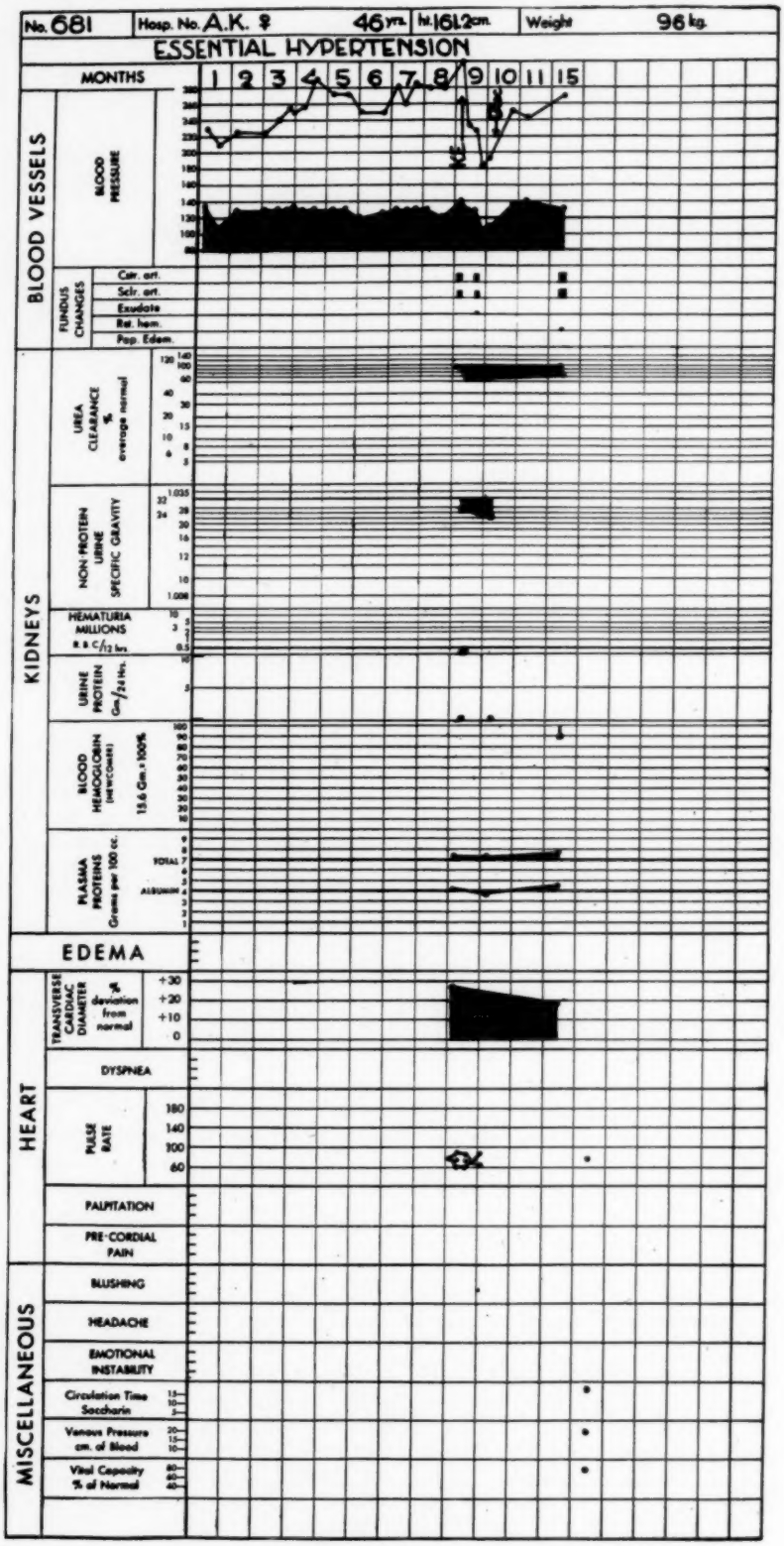
During the course of treatment two shock-like reactions and four bouts of back and chest pain with chills and fever have occurred.

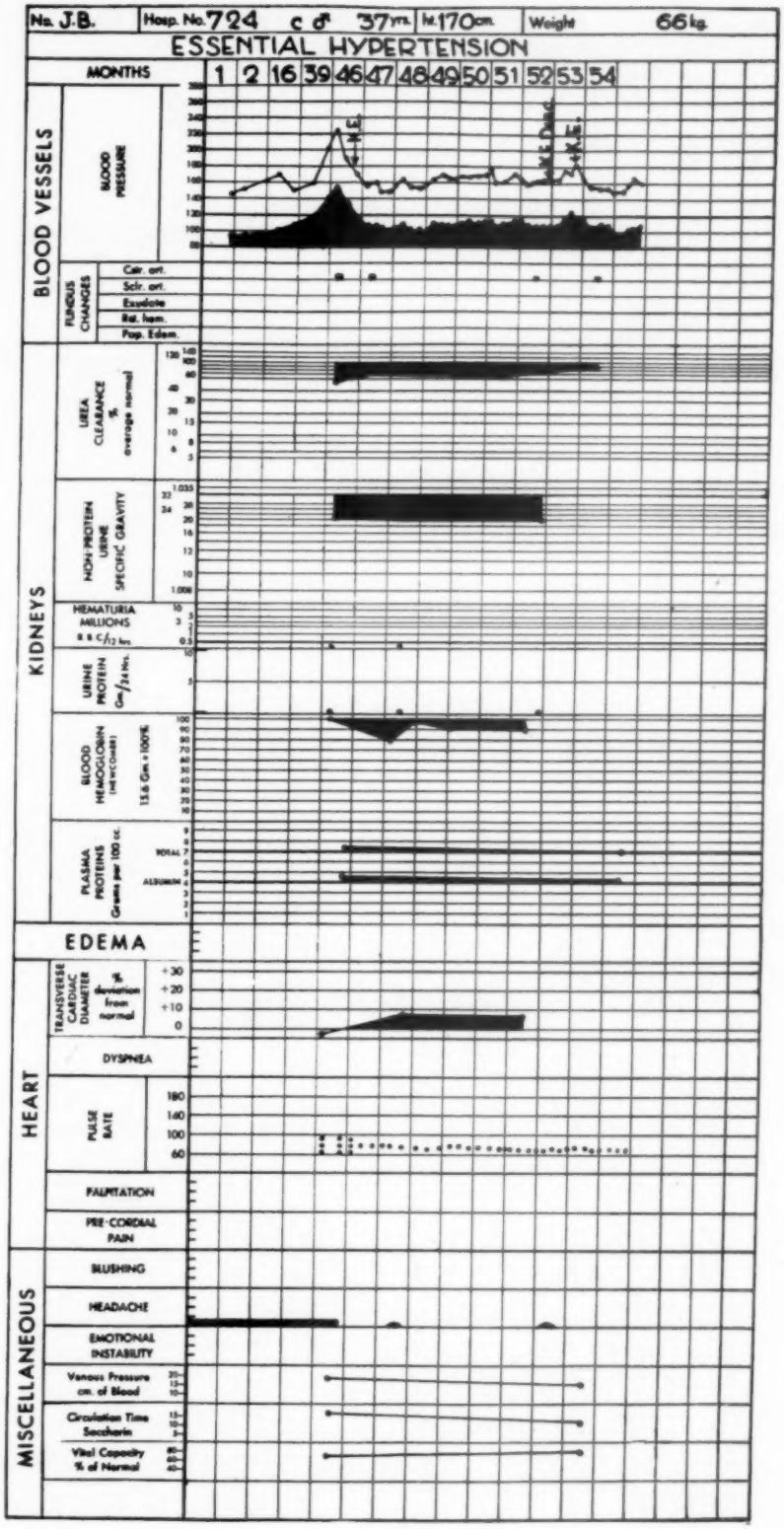
Case 16. A. K. (681). This white female, aged 46 years, complained of headaches, nervousness, pain over the heart, edema of the legs, and cramping in the feet and legs of a year's duration. Five years ago she passed through the menopause. Shortly before admission, vision in her left eye suddenly became blurred, and she was unable to see with her right eye.

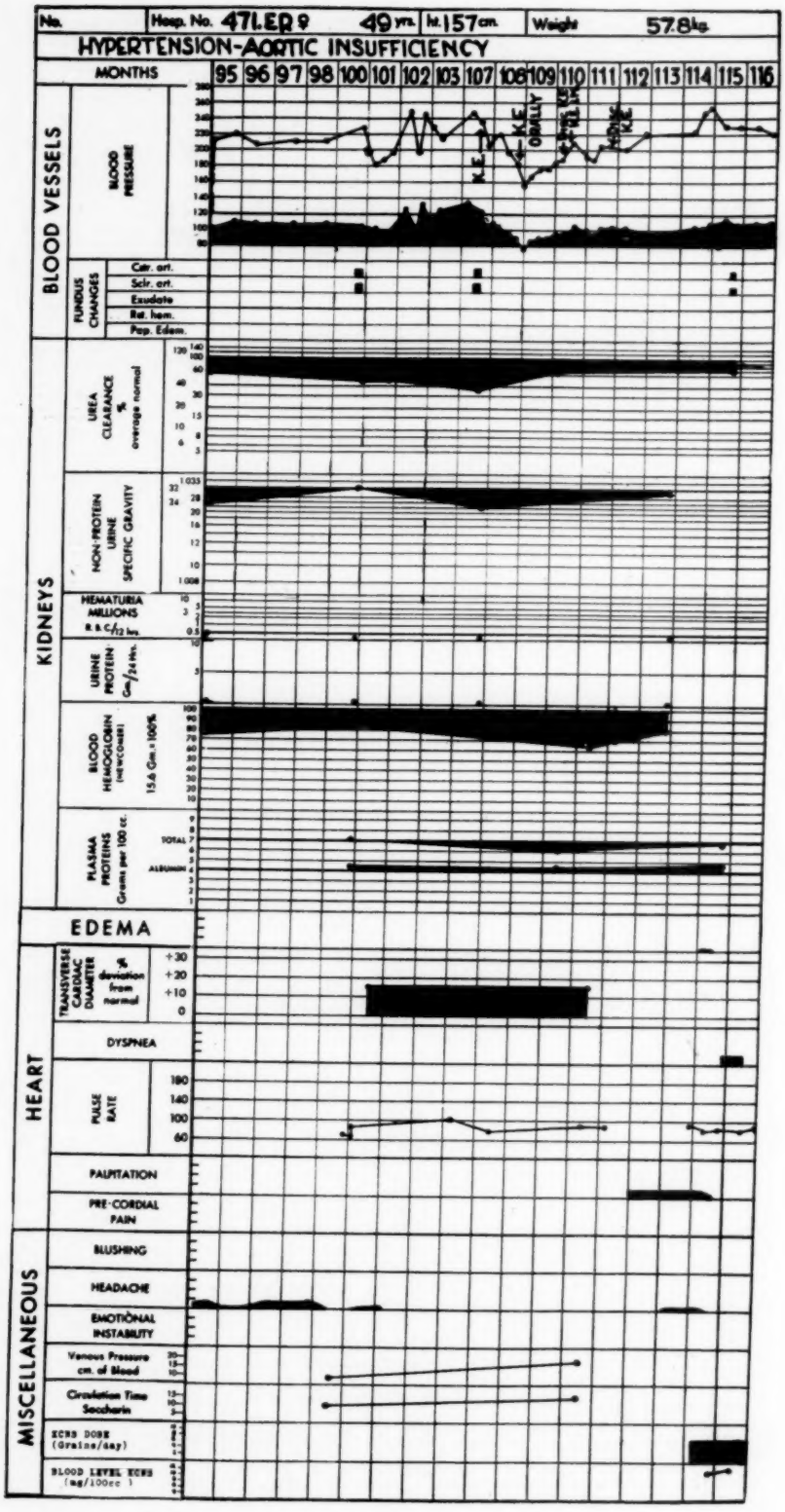
Physical examination revealed grade 2 constriction and sclerosis of the retinal arterioles. In the right retina there was a circular hemorrhagic area with a small patch of exudate. The heart was enlarged (+ 27 per cent deviation). Grade 1 edema was present over the ankles.

Urea clearance averaged 70 per cent of normal, and maximal ability to concentrate urine was 1.029. Some white blood cells were seen in the urine. A retrograde pyelogram revealed normal kidneys; urine culture was negative. The T-waves in Leads I, II, and III were inverted, and the S–T segment was depressed.

During the 16 day control period, the blood pressure averaged 237 mm. Hg systolic and 130 mm. diastolic. Renal extract was then administered, and during the next four days the average was 183 mm. Hg systolic and 100 mm. diastolic. A second extract was then employed for four days, and the blood pressure averaged 189 mm. Hg systolic and 107 mm. diastolic. The average while receiving a third extract was 189 mm. Hg systolic and 109 mm. diastolic. Still a fourth extract was used, and the average pressure was 189 mm. Hg systolic and 102 mm. diastolic. Extract was then discontinued, and the blood pressure rose to an average of 248 mm. Hg systolic and 132 mm. diastolic during a control period of 26 days.


No. 681
Hosp. No. A.K. ♀
46 yrs.
ht. 161.2 cm.
Weight
96 kg.
ESSENTIAL HYPERTENSION
MONTHS
1 2 3 4 5 6 7 8 9 10 11 15
BLOOD VESSELS
BLOOD PRESSURE
FUNDUS CHANGES
Cer. art.
Sclr. art.
Exudate
Ret. hem.
Pap. Edem.
KIDNEYS
UREA CLEARANCE % average normal
NON-PROTEIN URINE SPECIFIC GRAVITY
HEMATURIA MILLIONS R.B.C./12 hrs.
URINE PROTEIN Gm./24 Hrs.
BLOOD HEMOGLOBIN (Haldane) 13.6 Gm. = 100%
PLASMA PROTEINS Grams per 100 cc.
TOTAL
ALBUMIN
EDEMA
HEART
TRANSVERSE CARDIAC DIAMETER % deviation from normal
+30
+20
+10
0
DYSPNEA
PULSE RATE
180
140
100
60
PALPITATION
PRE-CORDIAL PAIN
MISCELLANEOUS
BLUSHING
HEADACHE
EMOTIONAL INSTABILITY
Circulation Time Saccharin
Venous Pressure cm. of Blood
Vital Capacity % of Normal


No. J.B.
Hosp. No. 724
c ♂
37 yrs.
ht. 170 cm.
Weight 66 kg.
ESSENTIAL HYPERTENSION
MONTHS
1 2 16 39 46 47 48 49 50 51 52 53 54
BLOOD VESSELS
BLOOD PRESSURE
H.E.
H.E. Decr.
H.E.
FUNDUS CHANGES
Cer. art.
Sclr. art.
Exudate
Ret. hem.
Pap. Edem.
KIDNEYS
UREA CLEARANCE % average normal
NON-PROTEIN URINE SPECIFIC GRAVITY
HEMATURIA MILLIONS R B C/12 hrs.
URINE PROTEIN Gm./24 hrs.
BLOOD HEMOGLOBIN (Haycroft) 15.6 Gm. = 100%
PLASMA PROTEINS Grams per 100 cc.
TOTAL
ALBUMIN
EDEMA
HEART
TRANSVERSE CARDIAC DIAMETER % deviation from normal
+30
+20
+10
0
DYSPNEA
PULSE RATE
180
140
100
60
PALPITATION
PRE-CORDIAL PAIN
MISCELLANEOUS
BLUSHING
HEADACHE
EMOTIONAL INSTABILITY
Venous Pressure cm. of Blood
Circulation Time Saccharin
Vital Capacity % of Normal


No.
Hosp. No. 471.ER 9
49 yrs.
ht. 157 cm.
Weight 57.8 kg
HYPERTENSION-AORTIC INSUFFICIENCY
MONTHS
95 96 97 98 100 101 102 103 107 108 109 110 111 112 113 114 115 116
BLOOD VESSELS
BLOOD PRESSURE
K.E.
K.E. DRILLY
FUNDUS CHANGES
Cer. art.
Sclr. art.
Exudate
Ret. hem.
Pap. Edem.
KIDNEYS
UREA CLEARANCE % average normal
NON-PROTEIN URINE SPECIFIC GRAVITY
HEMATURIA MILLIONS R.B.C./12 hrs.
URINE PROTEIN Gm./24 Hrs.
BLOOD HEMOGLOBIN (HELLIGE) 15.6 Gm. = 100%
PLASMA PROTEINS Grams per 100 cc.
TOTAL
ALBUMIN
EDEMA
HEART
TRANSVERSE CARDIAC DIAMETER % deviation from normal
+30
+20
+10
0
DYSPNEA
PULSE RATE
180
140
100
60
PALPITATION
PRE-CORDIAL PAIN
MISCELLANEOUS
BLUSHING
HEADACHE
EMOTIONAL INSTABILITY
Venous Pressure cm. of Blood
Circulation Time Saccharin
ECBS DOSE (Grains/day)
BLOOD LEVEL ECBS (mg/100cc)

Case 17. J. B. (724). This 37-year-old negro complained of occipital headaches for the past three years. Four years ago his blood pressure was normal, but two years ago it was 170 mm. Hg systolic and 100 mm. diastolic. Several members of his family are hypertensive.

On admission the blood pressure was 220 mm. Hg systolic and 130 mm. diastolic and, except for grade 1 constriction of the retinal arterioles, the physical examination was negative. Retrograde pyelograms showed no abnormalities. Electrocardiogram was normal, as were the other laboratory examinations. The cold pressor test caused the blood pressure to rise from 186 mm. Hg systolic and 130 mm. diastolic to 256 mm. Hg systolic and 180 mm. diastolic, and the 'Seconal' (Sodium propyl-methyl-carbinyl allyl barbiturate, Lilly) test caused a fall from 230 mm. Hg systolic and 138 mm. diastolic to 130 mm. Hg systolic and 100 mm. diastolic.

Renal extract was administered after the average pressure was established at 182 mm. Hg systolic and 123 mm. diastolic while the patient was in bed. After four days the patient was discharged from the clinic and received the injections daily as an out-patient. Since the patient was ambulant, the pressures would probably have been lower had he been confined to bed, as during the control period. The first week the average was reduced to 155 mm. Hg systolic and 106 mm. diastolic; the next week 160 mm. Hg systolic and 107 mm. diastolic; the third week 157 mm. Hg systolic and 109 mm. diastolic; and the fourth week 148 mm. Hg systolic and 103 mm. diastolic.

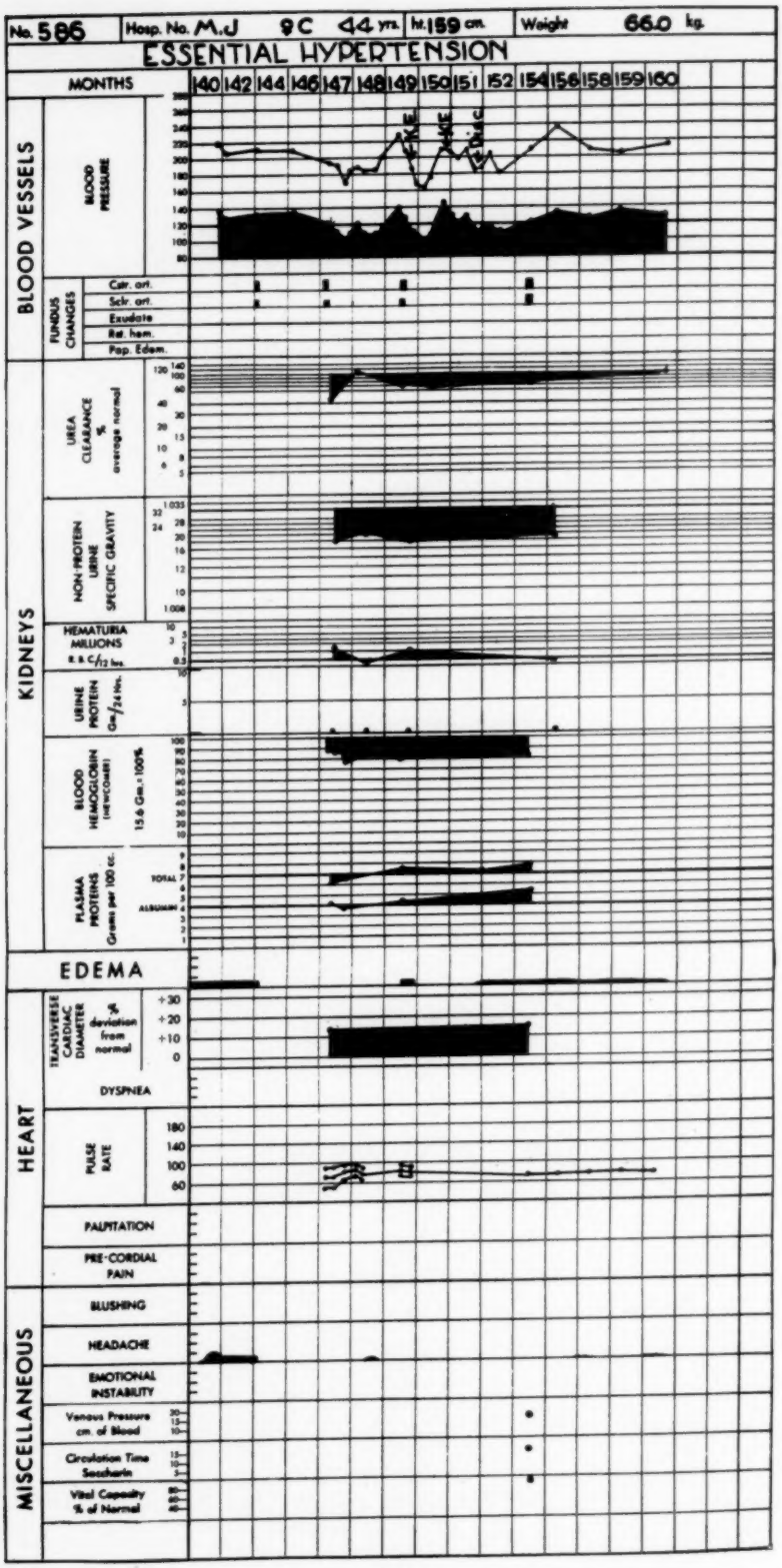
Arterial blood pressure was maintained at these levels for four months. He was symptom free and returned to work as a laborer. He had one shock-like reaction in this time. Kidney extract was discontinued for three weeks. Arterial blood pressure rose to an average of 171 mm. Hg systolic and 119 mm. diastolic. During this period he lost five pounds in body weight and headaches recurred. Kidney extract was administered, and arterial pressure was maintained at averages of 148 to 156 mm. Hg systolic and 99 to 109 mm. Hg diastolic.

Case 18. E. P. (741). This 49-year-old colored woman complained of headaches, dizziness, and dyspnea on exertion for the past seven years. Hypertension was found at that time. Since then the blood pressure has remained elevated, ranging from 200 to 270 mm. Hg systolic and 120 to 180 mm. Hg diastolic.

Physical examination showed grade 2 constriction and sclerosis of the retinal arteries. The heart was enlarged (+15 deviation), and there was a diastolic blow heard at the base. The electrocardiogram showed left axis deviation, slight inversion of the T-wave in Lead I, and an S-wave was present in Lead II. She is known to have had syphilis since 1935 and received sufficient treatment to alter the Wassermann reaction from positive to negative. The gold curve of the spinal fluid was that of paresis. Retrograde pyelograms were negative. The patient was treated in the out-patient clinic and was not confined to bed.

During the control period the blood pressure averaged 229 mm. Hg systolic and 119 mm. diastolic. The first two weeks after injection of kidney extract the pressure average was 196 mm. Hg systolic and 98 mm. diastolic, the following two weeks 182 mm. Hg systolic and 90 mm. diastolic, and the next week 157 mm. Hg systolic and 78 mm. diastolic. The site of the injection in the buttocks became swollen, and an abscess developed. Hence the extract was given, in five times the parenteral dosage, by mouth. The blood pressure averages for each succeeding week were 168/85 mm. Hg, 177/91 mm. Hg, 178/91 mm. Hg and 184/96 mm. Hg. Extract was discontinued, and the average for the week was 210/104 mm. Hg. For the next two weeks injections of extract were given at irregular intervals, and the blood pressure average was 186/92 mm. Hg.

Case 19. M. J. (586). This patient, a colored female, aged 44 years, complained of headaches, vertigo, and dyspnea occasionally. Hypertension is believed to have occurred for the first time during her seventh pregnancy eleven years ago, and


No. 586
Hosp. No. M.J
9C
44 yrs.
ht. 159 cm.
Weight 66.0 kg.
ESSENTIAL HYPERTENSION
MONTHS
140 142 144 146 147 148 149 150 151 152 154 156 158 159 160
BLOOD VESSELS
BLOOD PRESSURE
FUNDUS CHANGES
Calr. art.
Sclr. art.
Exudate
Ret. hem.
Pap. Edem.
KIDNEYS
UREA CLEARANCE % average normal
NON-PROTEIN URINE SPECIFIC GRAVITY
HEMATURIA MILLIONS R. B. C./12 hrs.
URINE PROTEIN Gm./24 hrs.
BLOOD HEMOGLOBIN (NEWCOMER) 13.6 Gm. = 100%
PLASMA PROTEINS Grams per 100 cc.
TOTAL
ALBUMIN
EDEMA
HEART
TRANSVERSE CARDIAC DIAMETER % deviation from normal
+30
+20
+10
0
DYSPNEA
PULSE RATE
180
140
100
60
PALPITATION
PRE-CORDIAL PAIN
MISCELLANEOUS
BLUSHING
HEADACHE
EMOTIONAL INSTABILITY
Venous Pressure cm. of Blood
Circulation Time Saccharin
Vital Capacity % of Normal

eight years ago her blood pressure was found to be 150 mm. Hg systolic and 88 mm. diastolic. Three years ago it had risen to 200 mm. Hg systolic and 140 mm. diastolic.

On admission to the Lilly Clinic grade 2 constriction and grade 1 sclerosis of the retinal arteries were observed. The thyroid gland was diffusely enlarged (grade 1). The electrocardiogram showed left axis deviation. Urea clearance varied from 82 to 93 per cent of normal. Maximal ability to concentrate urine was 1.026. The Addis count was normal, as were the plasma proteins. The heart was slightly enlarged (+13 deviation). The retrograde pyelogram was normal except for slight dilatation of a calyx on the left side. The blood pressure during her stay of 50 days averaged 213 mm. Hg systolic and 123 mm. diastolic. As an out-patient the pressure average was 220 mm. Hg systolic and 130 mm. diastolic.

The patient was readmitted 10 months later. Sclerosis of the retinal arterioles was now graded 2 and constriction graded 3. The liver was palpable below the costal margin. The maximum ability to concentrate urine was reduced (1.018 to 1.021). Urea clearance was 103 per cent. The deviation from normal cardiac size was +15 per cent.

Blood pressure during the control period averaged 190 mm. Hg systolic and 114 mm. diastolic. The first kidney extract, given for a period of seven days, caused no significant fall in pressure (191 mm. Hg systolic and 110 mm. diastolic). The second extract, given for four days, was associated with a fall (170 mm. Hg systolic and 106 mm. diastolic average). Extract was discontinued, and the pressure rose to 200 mm. Hg systolic and 114 mm. diastolic.

The patient was again readmitted a month later. This time, during the control period of one week, the arterial pressure average was 210 mm. Hg systolic and 125 mm. diastolic. Renal extract was started, and for the next eight days the pressure fell to an average of 169 mm. Hg systolic and 110 mm. diastolic, at times being as low as 140 mm. Hg systolic and 90 mm. diastolic. During the next three weeks five different batches of extract were given. The blood pressure average was 175 mm. Hg systolic and 99 mm. diastolic, occasionally falling to low levels (132 mm. Hg systolic and 84 mm. diastolic). The patient felt well throughout the period she received extract, except for relatively slight pain around the site of the injections.

Extract was discontinued and the patient received treatment in the out-patient clinic. The blood pressure has varied between 204 and 236 mm. Hg systolic and 120 and 140 mm. Hg diastolic for 12 months.

Clinical Results Summarized

1. *Effect on Arterial Pressure.* At the outset it must be realized that in most patients the extracts have been prepared by varying methods. During the early part of our work it seemed desirable to employ only slight modifications of the standard ammonium sulfate fractional precipitation method. We determined also to employ only the parenteral method of administration for several reasons not the least of which was that Harrison, Grollman and Williams [26] are making an exact study of extracts when given by mouth. They were the first to show that their extract is effective when administered by this route.

Many variations have been introduced into our method for preparing renal extracts with the hope that greater purity would be achieved. The result has often been that the potency has been either reduced or lost.

Administration of renal extracts intramuscularly, daily, for a week or more is usually followed by only slight reduction in average blood pressure.

Continued administration leads to a progressive fall until normal or near normal levels are reached. If the extract is discontinued in most patients the pressure begins to rise within several days to a week. From our experience with the small group of 19 patients who have received prolonged treatment, our present opinion is that patients in whom the neurogenic component seems marked do not respond as quickly as do those in whom it is not so evident. Once the pressure is reduced it is maintained with smaller amounts of extract.

TABLE II

The Effect of Injection of Kidney Extract on T-Wave Changes, Dyspnea, Vital Capacity, Venous Pressure and Circulation Time

Malignant Hypertension

	Hosp. No.	T-Wave Changes		Circulation Time in Seconds Saccharin		Venous Pressure in cm. Blood		Dyspnea	
		Before, Inverted in Leads	After Upright	Before	After	Before	After	Before	After
1	703	I, II	All leads	17	9	21	9	0	0
2	769	Not inverted	All leads	18	9	10.5	7.5	0	0
3	764	I, II, IV	All leads	13	11	7.75	11	++	0
4	671	I, II	All leads	7	9	7	9	+	0
5	662	I, II, IV	Unchanged	24	14	14	9	++++	++
6	553	Not inverted	All leads	33	21	15	17	+	+
7	683	Not inverted	All leads	—	—	5	—	+++	0
8	722	I, II, IV	Lead I	20	20	21	17	+	0
9	730	I, II, IV	II, III, IV	30	15	20	10	+	0
10	742	I, II	All leads	25	15	18	7.5	++	0
11	766	Not inverted	All leads	11	11	16.75	30	0	0
12	746	I	All leads	18	18	8.5	8.5	0	0
13	750	Not inverted	All leads	16	20	11	13½	+	+
		Essential Hypertension							
14	726	Not inverted	All leads	17	16	7	8.5	++	0
15	757	I, II, IV	Biphasic in I, II, IV	31	13	13	11.5	0	0
16	681	I, II, IV	II, III, IV	—	18	—	18	0	0
17	724	Not inverted	All leads	17	12	18	15	0	0
18	471	I	All leads	10	15	9	17	0	0
19	586	I, II, III	All leads	—	16	—	18	0	0

The length of time the patient has suffered from hypertension does not, within limits, appear to affect greatly the ease with which blood pressure is reduced. The arterial pressure of 2 of the 19 patients has been quite difficult to depress even moderately.

The diastolic pressure usually falls proportionately more than does the systolic pressure. It is not unusual to maintain the diastolic pressure in the range 80 to 110 mm. Hg while the systolic is 160 to 200 mm. Hg. This we interpret as being due to preëxisting arteriosclerosis, the typical hemodynamic picture of the latter appearing when that due to humorally produced hypertension is partially resolved.

Patients suffering from the malignant syndrome appear to respond well to administration of renal extract. The level of arterial pressure is no more difficult to depress than in some patients with benign hypertension. We wish, however, to emphasize that we make no pretense of presenting quantitative studies on the effectiveness of extracts in different types of hypertension.

2. *Effect on the Heart.* The size of the heart, as estimated from measurement of the transverse cardiac diameter in roentgen-ray films, is reduced when the blood pressure is reduced. When the T-waves in Leads I and II were inverted they have been restored to their upright position (table 2). This has occurred in five patients with malignant hypertension and two with essential hypertension. One patient with terminal malignant hypertension and one with essential hypertension treated five weeks have shown no alteration. Circulation time as measured by injection of saccharin is somewhat decreased in some of the patients, especially when it has been grossly abnormal before treatment. Dyspnea has been lessened when present. It would be hazardous to state that the moderate but general improvement in cardiac function will be maintained on the basis of only a year and a half's experience. The continuity of this experience is, of course, marred from the clinical point of view by constant experimentation with new types of extract.

3. *Effect on the Kidneys.* Urea clearance does not appear to be greatly influenced when the blood pressure falls as the result of kidney extract. This was not unexpected as Page [27] found no significant changes when the arterial pressure fell spontaneously in patients or was reduced by extensive sympathectomy or administration of potassium thiocyanate. In the six patients with essential hypertension studied by Corcoran and Page,[19] there was a rise of renal blood flow of the order of 40 per cent in three, and half that amount in the others. Definite evidence of efferent arteriolar relaxation was found as measured by the fall of filtration fraction. The increase of flow in the nine patients with malignant hypertension was not as marked, averaging about 15 per cent, but the relaxation of the efferent arteriole was proportionately greater.

The ability of the kidneys to concentrate urine was determined by the specific gravity corrected for the protein content of the urine of a specimen taken in the last 12 hours of a 24 hour period without fluids (Addis test). Ten patients showed no significant change after several months of treatment. In five there has been a decline and in four an increase.

4. *Ocular Changes.* The improvement of vision in patients with malignant hypertension is one of the most dramatic results of administration of kidney extract. Improvement may occur within several days or weeks.

Examination of the fundus shows that only moderate visible relaxation of the constricted arterioles occurs and almost no alteration in the visible changes interpreted by us as arteriolosclerosis. The disappearance of hemor-

TABLE III

Estimated Changes in Eyegrounds After Treatment with Kidney Extract

		Arterial Constriction		Sclerosis		Exudates		Hemorrhages		Papilledema	
		Before	After	Before	After	Before	After	Before	After	Before	After
						Malignant Hypertension					
1	703	+++	++	++	+	+++	0	++	0	+++	0
2	769	++++	+++	++++	++++	++++	+	++++	+	++++	++
3	764	++++	+++	++++	++++	+	0	+++	0	+	0
4	671	++	+	++	++	+	0	+	0	+	0
5	662	+++	+++	+++	+++	+++	+	+++	+	+++	0
6	553	+++	++	++	+	0	0	0	0	0	0
7	683	+++	+++	+++	+++	+++	+++	+	0	+++	+
8	722	++++	+++	++++	+++	+++	0	+++	0	+++	±
9	730	+++	+++	+++	+++	0	0	+	+	+	0
10	742	+++	++	++	+	++	0	+	0	++	0
11	766	++++	++	+++	+++	0	0	0	0	++	+
12	746	+++	+++	+++	+++	+	0	+	0	+	0
13	750	+++	+++	++++	++++	0	0	+	0	+	0
						Essential Hypertension					
14	726	++	+	++	++	0	0	0	0	0	0
15	757	+++	++	++	++	0	0	0	0	0?	0
16	681	++	++	++	++	0	0	0?	0?	0	0
17	724	+	+	0	0	0	0	0	0	0	0
18	471	++	++	++	++	0	0	0	0	0	0
19	586	+++	+++	++	++	0	0	0	0	0	0

rhage, exudates and papilledema is the most marked and characteristic feature of the regressive changes occurring when extract is given.

5. *Urine and Blood Changes.* The number of red blood cells in the urine as ascertained by the Addis count is often sharply diminished after administration of kidney extract. Profuse hematuria was unaffected in one patient with malignant hypertension who subsequently died. Proteinuria may be reduced simultaneously with reduction in hematuria.

TABLE IV

The Effect of Kidney Extract on the Number of Red Cells in the Urine, Proteinuria, Blood Hemoglobin and Plasma Proteins

		Addis Count in Urine				Hemoglobin in per cent		Plasma Proteins, grams/100 c.c.	
		Hematuria, millions RBC in 12 hrs.		Proteinuria, Gm./24 hrs.					
		Before	After	Before	After	Before	After	Before	After
		Malignant Hypertension							
1	703	0.5	0.2	8.5	5.0	50	65	5.2	6.1
2	769	.06	.06	.2	.04	90	84.4	6.1	6.0
3	764	.8	.5	.8	.1	70	60	6.6	6.9
4	671	1.5	0.1	0.5	0.5	60	60	6.5	7.5
5	662	0.4	0.1	2.0	1.8	68	68	5.2	6.5
6	553	3.0–	0.6	0.5	0.1	90	70	6.5	6.5
7	683	2.0	10.0	3.0	1.0	70	58	6.3	4.5
8	722	0.6	0.3	3.0	0.5	65	65	7.60	7.5
9	730	0.21	0.28	2.5	.37	80	61	6.65	6.56
10	742	0.2	0.2	0.2	0.2	80	80	6.20	7.2
11	766	0.3	0.3	0.3	0.3	82	66	6.15	6.69
12	746	0.2	0.5	0.7	0.5	85	85	6.67	6.67
13	750	0.1	0.1	1.5	1.0	50	77	5.0	6.2
		Essential Hypertension							
14	726	0.4	0.2	0.142	.1–	85	91	6.0	5.86
15	757	0.2	—	1.0	—	92	77	6.6	6.0
16	681	0.1–	0.1	0.1	0.1	90	90	7.3	7.7
17	724	0.1–	0.1	0.1	0.1	98	95	7.3	7.5
18	471	0.2–	0.15	0.5	0.5	82	80	7.0	6.5
19	586	1.0–	0.3	0.2	0.2	80	82	7.5	7.7

The change in hemoglobin in patients with malignant hypertension is of especial interest because during the usual course of events the loss is rapid and often indicates roughly the prognosis (see Page [28] for charts of typical untreated cases). After adequate treatment with extract the progressive fall is usually checked. In two of nine patients rise has occurred. Plasma proteins usually rise or are unchanged, the latter especially if they are already near the limits of normal.

Untoward Reactions to Kidney Extract

Two sorts of severe reactions to injection of renal extract are encountered. During the first, generalized flushing of the skin and lacrimation occur. The patient complains of a stinging sensation usually spreading from the face downwards. The blood pressure falls, dyspnea occurs and retrosternal pain or choking is felt. The patient is pale, perspiring, and the extremities are cold. The heart rate is slowed and abdominal cramps occur with passage of gas and stools. Edema of the face may appear. During such reactions adrenalin 1 : 10,000 solution is slowly administered. After termination of the reaction, fever lasting several hours occurs.

The second type of reaction is distinguished from the first especially by the fact that the blood pressure and pulse rate rise markedly rather than fall. The patient first complains of pain radiating from the site of injection up the back and down the legs. Spasm of the muscles, flushing and perspiration are observed. The reaction is over in from 3 to 7 minutes and is often relieved by injection intravenously of papaverine.

While these reactions are alarming, no after effects have occurred. The irregularity of the reactions is one of the most startling features. An extract which in sufficient dosage in most patients will elicit a reaction produces them only irregularly when the dose is reduced; but the same extract may, even in large doses, cause no reactions in some patients. In short, certain patients exhibit great resistance to reactions and even in the "reactors" their occurrence is erratic.

As purification has been carried farther, the incidence of reactions has been reduced but it still has to be reckoned with. For this reason, we have found it wise always to have an emergency tray containing 1 : 10,000 adrenalin in saline and ephedrin in syringes. If the adrenalin is administered at the very beginning of the reaction it may be all but avoided and so be the cause of only minor discomfort.

We have studied the records closely to ascertain whether any direct relationship exists between the occurrence of reactions and the fall in arterial pressure. For a day or more after a severe reaction the blood pressure may be, but is not necessarily, depressed. But depression of blood pressure occurs without reactions so it would be incorrect to attribute all or most of the depressor effects to reactions. In this connection it is of interest that reactions have never been observed in dogs or rats despite the fall in blood pressure.

The occurrence of these reactions shows that the preparation and administration of kidney extract are in the experimental stage. Effort is being made at the present time to purify the extracts sufficiently so that they will not occur.

Discussion

Sufficient experimental evidence appears to demonstrate that arterial blood pressure can be reduced by parenteral administration of kidney extract in dogs and rats with renal hypertension and patients with essential and malignant hypertension. If administration of the extract is discontinued the blood pressure, after a variable length of time, rises.

The occurrence of reactions to the injection of extract in patients has been a disturbing side-effect, and they would not occur if given by mouth as recommended by Harrison, Grollman and Williams. We have not employed this method of administration because the latter workers are making a thorough study of it and because we believe a need might be found for a sufficiently pure extract for parenteral use. It would seem reasonable to suppose that reactions are due to sensitivity to foreign protein. Their highly irregular occurrence in so-called "reactor" patients lends no especial support to this view. Non-reactor patients are those in whom reactions are not induced by extracts which may cause sharp ones in the reactor type. It is of interest that there is a rough quantitative relationship between the amount of extract administered and the severity of the reaction. This suggests that the reactions are produced by impurities. There does not appear to be any direct relationship between the occurrence of reactions and the prolonged fall in blood pressure.

We have observed in human beings and in dogs that the amount of extract required initially to lower blood pressure varies, in some instances, markedly. When the fall begins it may progress rapidly, i.e. within three to five days in dogs, and in several weeks in patients. This suggests the possibility that before decline in arterial pressure may be expected, depleted reservoirs in the body must be filled, and it is only then that reduced arterial pressure results.

The observation of Corcoran and Page [19] that angiotonin causes efferent arteriolar constriction with reduction of renal blood flow, which may be abolished by injection of kidney extracts, suggests some degree of specificity in the hypotensive action of these extracts. The pressor action of angiotonin as well is dampened or abolished. The evidence, we believe, is insufficient at present to determine the mechanism by which renal extracts reduce blood pressure.

Experience in the treatment of patients for the past year and a half suggests that the extracts might have merit. The yields of active material are low and the difficulty with reactions has been only partially overcome. It is therefore, not a practical treatment at the present time. Its use only in research clinics appears justified.

Summary

1. A study has been made of the effects of parenteral injections of extracts of whole kidneys on 280 hypertensive dogs, 13 patients with malignant hypertension and 6 patients with essential hypertension. Some of the patients have been treated for about a year.

2. Arterial blood pressure has been significantly reduced and other objective as well as subjective signs of improvement have occurred sufficient to justify further experimentation in research clinics.

3. Because of occasional shock-like reactions and the lack of standard chemical procedures which yield a uniform product of high potency, it cannot at present be considered a practical treatment.

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RESULTS FROM THE MANAGEMENT OF BLEEDING GASTRIC AND DUODENAL ULCER*

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The purpose of this presentation is to direct attention to a dramatic improvement in some of the recently reported results from the treatment of profusely bleeding gastric and duodenal ulcer. This has followed the application to that emergency of a principle already well established in the management of uncomplicated ulcer: that of prompt, frequent and reasonably adequate feeding. Designed originally by Lenhartz and by Sippy to control the restlessness and the acidity of the empty stomach and so promote simple ulcer healing, the therapy based on this principle also tends, in the bleeding case, to stop the hemorrhage and, when combined with a sufficient fluid intake, to prevent or combat shock. As now employed in ulcer hemorrhage it consists primarily in the oral administration, beginning as soon as the patient comes under observation, even if still bleeding, and at frequent intervals thereafter, of an ample supply of non-irritating food and of fluid; secondarily, and varying with the inclination of the physician, it may include the use of alkalies, of hematinics, of sedatives and of transfusions. A measure of its practical value lies in the available statistics which indicate that the death rate from bleeding ulcer on the prompt feeding program has dropped to about one third what it was on the older and more commonly used starvation regimen.

The literature on the results obtained by the previously accepted method of medical management, that of immobilization, morphine and starvation during and for several days after the cessation of hemorrhage, gives an average mortality rate, for 5843 collected cases, of 8.7 per cent,[1] for some series as high as 25 per cent.[2] Even in the Scandinavian countries, where most cases even with minor hemorrhage are hospitalized, it has ranged from 7 to 10 per cent. Furthermore, one finds that the most favorable report on the surgical management of bleeding ulcer, that of Finsterer,[3] gives a mortality rate of 6 per cent, others as high as 100 per cent; the average for 383 collected cases has been reported as 28 per cent.[1] One, of course, admits that many of the patients were operated upon only after all hope of cure by medical measures had passed, but that was not true of Finsterer's series. On the other hand, a complete review of the literature shows that for approximately 1400 cases of massive hemorrhage from ulcer, treated by prompt and adequate feeding, the gross mortality rate is only 3 per cent.[4]

Meulengracht[5] very properly is given credit for the development of the prompt feeding program for hemorrhage, but six years previously Andre-

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sen,[6] a Fellow of this College, outlined and recommended, on the basis of the same physiological principles and personal observations, that the administration of a solution of gelatin, orange or grape juice and lactose be started immediately after the cessation of the hemorrhage. Unfortunately he presented no results from that type of therapy, but in 1939 he[7] did report on a series of 120 severely bleeding cases, having employed in them milk and cream in addition to his gelatin mixture and having started the feedings in the midst of the hemorrhage; the mortality rate in that series was 5 per cent.

It was only eight years ago that Meulengracht[5] made his first report on this type of management, having had a mortality of 1.8 per cent in 109 cases. Later, in 1939, his gross mortality for 491 severely bleeding cases was 2 per cent.[8] His program provides for the feeding of the patient from the onset of his hemorrhage and gives him, in six feedings, along with alkalies and iron, a full and well balanced diet, including milk, cereals, eggs, sliced and ground meats, cheese, mashed potatoes, pureed green vegetables, white bread, stewed fruits, tea and cocoa. He evolved the technic as a result of his observations, amply confirmed by other clinicians, that exhausted patients often die of gastric hemorrhage in spite of scrupulous dieting, that some patients with protracted hemorrhage do not stop bleeding until fed and that some patients with profuse hemorrhage and without special variation in their diet recover; also, of his personal conviction that peptic ulcer healing is not promoted by starvation, a stomach empty but for its own acid secretion or a diet deficient in calories and vitamins.

Witts,[9] of St. Bartholomew's, in reporting in 1937 on 27 cases of bleeding from the stomach and duodenum treated by prompt feeding, ably presented additional arguments in favor of that type of management and emphasized the importance at the same time of an adequate intake of fluid. He especially referred to the significance of Blalock's[10] experimental work on post-hemorrhagic shock in this connection and pointed out that death in the profusely bleeding cases results more often from shock than from exsanguination. He also called attention to the work of Cullinan and Price,[11] which showed that gastric hemorrhage is more likely to occur after starvation, and to the belief of Hunter that a free flow of saliva assists in clot formation. Subsequently Jones,[12] from Witts' clinic, reported on 50 bleeding ulcer cases, including those in the original series and all treated by prompt feeding, with but one death, that of a 69-year-old woman who had in addition a severe erosive gastritis. The treatment was the same as Meulengracht's except that the food was more liquid, totalled about 2750 c.c. per day and included 2500 to 3500 calories; also a plentiful supply of vitamins. No alkalies or other drugs were allowed, and transfusions were reserved for obvious shock.

More recently Woldman,[13] who developed the method of treating uncomplicated gastric and duodenal ulcer by a continuous intragastric drip of a solution of aluminum hydroxide, has applied that method together with

second-hour bland feedings in the management of massive bleeding from ulcer. He lost only three cases out of a total of 144 (2.1 per cent), and attributes his results entirely to the neutralization of the acid gastric juice by the aluminum preparation. Since, however, his results are no better than those obtained by the use of the prompt feeding program alone, which he also employed, one must await further comparative studies as to the influence of the aluminum hydroxide. Lineberry and Issos [14] got even better results, with no mortality, in a series of 36 cases treated by the formal Sippy regimen begun in the midst of the hemorrhage.

My personal experience with the prompt and adequate feeding program for massive hemorrhage from gastric and duodenal ulcer has been limited to 32 cases, which are being reported separately by Nicholson and Miller.[4] Of these but one patient died: a man who subsequently was found to have had at the same time a duodenal perforation. The average hemoglobin reading for the series was 44 per cent. Twelve of the patients, before being seen by one of our staff members, had been starved and given morphine, but otherwise all of them, on admission to the hospital, were promptly put on six feedings a day of an ample smooth diet, usually without meat for the first 24 hours, and given only sodium phenobarbital as a sedative; no alkalies or iron. A blood transfusion was given to 11 subjects. In some of the cases the bleeding apparently had stopped before the feeding was begun; in others it ceased quite promptly; in still others it persisted for several days, in one for a week and yet without the development of shock.

As one reviews the various reports he is impressed by the fact that some of the cases were hopeless from the beginning. Autopsy often revealed a large eroded artery, and in many of them the artery was in the base of an old calloused ulcer which tended to prevent its closure. Some were hospitalized late in the hemorrhage when almost exsanguinated and died before any form of treatment could be given a trial; this was true of four of the 10 fatal cases in Meulengracht's series. All of these, however, have been included in the quoted mortality figures. If all the fatal cases that were practically exsanguinated and moribund before the treatment was inaugurated, those with perforation, like our own, Jones' single fatal case with extensive erosive gastritis and three of Andresen's cases, which he believed died as a result of excessive transfusions, are eliminated, the mortality from the feeding program is reduced to slightly less than 2 per cent.[4]

In view of such a low mortality rate from the medical management of bleeding ulcer one naturally wonders if surgical interference is ever justified. It is appreciated that if one could judge accurately from the beginning what patients would not recover on a medical program, an occasional one of them might be saved by prompt surgery. Such a selection, however, is obviously impossible, and if any one of those, who otherwise would have recovered, should be operated upon he is subjected to a fair chance of losing his life. This consideration, together with the fact, as pointed out by Witts, that the

best individual medical results are far superior to the best individual surgical results for any group of patients, leads me to believe that none of them in the midst of the hemorrhage, unless an additional complication such as perforation is diagnosed, should be managed surgically.

Although the reduction in the mortality rate is the most convincing factor in favor of the prompt and adequate feeding regimen for bleeding gastric and duodenal ulcer, everyone who has written on the subject has been equally impressed by its effects on the morale of the patient. Instead of being restless, agitated and frightened, he is calm, composed, comfortable and cooperative. Nausea rarely persists after beginning the feedings, and usually, if the treatment is begun early in the hemorrhage, the feeling of exhaustion, that formerly was provoked or at least maintained by his thirst, hunger and enforced immobility, is absent. Morphine usually is not required, and this in itself tends to maintain a more tonic condition of the gastric and duodenal musculature.[15] The patient, according to Witts, looks, feels and does well.

This brief review of some of the recent reports on the medical management of bleeding gastric and duodenal ulcer indicates (1) that far better results, both as regards the survival of the patient and his comfort, may be expected from a prompt and adequate feeding regimen, including plenty of fluid, than from the better known starvation program; (2) that the particular type of diet administered, so long as it is non-irritating, is of less importance than that it be given promptly and in adequate amount, and (3) that surgical intervention in the midst of the hemorrhage is rarely, if ever, justified.

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WEIL'S DISEASE; REPORT OF SIX CASES*

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Weil,[1] in 1886, described a disease characterized by jaundice and nephritis. Inada and his co-workers[2] in a remarkable series of reports delineated the clinical and pathological picture, described the etiological agent and named it *Spirochaeta icterohaemorrhagica.* Noguchi,[3] in 1917, reported the presence in American wild rats of a spirochete morphologically and immunologically identical with the Japanese and European strains. In 1918 he[4] further described the organism and called it *Leptospira icterohaemorrhagica.* Wadsworth et al.[5] described the first case in the United States which occurred as an accidental infection in a laboratory worker.

Noguchi[4] described the causative organism as a very tightly and regularly wound cylindrical filament tapering to sharply pointed ends. It usually assumes a graceful hook at one or both ends. The main portion is straight or slightly bent. The length of the organism varies from 3 to 40 micra. The distance between the apices of the adjacent spirals is 0.5 micron. There are about six spirals in each terminal portion. In the dark-field the organism is seen to be dotted with alternate bright and shadowy portions surrounded by a halo. The leptospira proceeds by a rotary motion and appears to be propelled from the rear by a rotating hook. The organism passes through a Berkefeld filter. Unlike other spirochetes it resists the destructive action of 10 per cent saponin. Schüffner in 1934[6] reported the isolation, from dogs and from one case in a human, of a morphologically similar but immunologically and epidemiologically somewhat different strain of leptospirae which he called *Leptospira canicola.* Several human cases due to this strain have since been reported.

It has been known for some time that the rat is the animal host and that the leptospirae are harbored in the animal's kidneys and excreted in the urine.[2, 3, 7, 8, 9, 10] Human infection usually results from contact with the infected urine, although it may rarely occur as a result of the bite of a rat.[2e, 2f] The disease has been found to occur most frequently in sewer workers,[11] miners,[2f] workers in rice fields,[2a] fish-workers,[12, 13, 14] and other occupations involving close contact with the urine of infected rats. Such contact takes place in a wet or damp environment. It also occurs following swimming or near drowning in contaminated water. A number of cases occur in which no clearcut history of such contact may be obtained.

The guinea-pig has been found to be very easily infected and therefore a satisfactory animal for experimental study of the disease. Small guinea-pigs

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(100 to 150 grams) should be used. Packchanian [15] found that certain species of American deer mice are also suitable animals but the ordinary laboratory white mice as well as rats may be carriers of the organism. The guinea-pig is rarely found to be spontaneously infected. Inada et al.[2a] stated that the leptospirae could pass through either the healthy or the abraded skin of guinea-pigs. Since in some of their patients local glandular enlargement was present, they concluded that the skin may sometimes be the point of entrance of the organism. Schüffner,[6] however, found that guinea-pigs could be infected by prolonged immersion in contaminated water only if their skins were scarified. He also found that the disease was considerably more frequent in humans who nearly drowned than in swimmers. He concluded that this was probably due to contact of the water with the bronchial and intestinal epithelium. Jorge [16] reported an epidemic arising from drinking water.

Inada [2g] divided the disease into three stages. This division is of practical importance since the laboratory procedures necessary in establishing the diagnosis give different results in the three stages. The first, or febrile stage is preceded by an incubation period varying between 4 and 19 days, usually between 7 and 13 days. During the first stage the leptospirae are circulating in the blood. There are no demonstrable antibodies in the blood at this time. The organism may be in the urine. The disease varies widely in its severity. There may be a severe chill followed by a high fever and headache. Chill is not always present, but, though the disease be mild or severe, the onset is usually sudden. Restlessness, apathy, delirium, or coma may be present. Muscular pains and tenderness are common and may be cramp-like and are most frequent in the thighs, back and calves; but may be in the abdominal wall and cause considerable confusion with acute intra-abdominal conditions. Anorexia, nausea, vomiting or diarrhea may occur. Prostration is frequently marked and may be out of proportion to the rest of the symptoms. Cough or hiccough may be present. Hyperemia of the conjunctivae is a common finding. The tongue may be red or thickly coated. There may be ulcers on it and on the mucous membranes of the mouth. The tonsils may be red and swollen. In an occasional case there is meningeal irritation. The white blood count is elevated and usually is less than 20,000 per cubic millimeter. Albumin, cells and casts are found in the urine at this time. The first stage lasts from four to seven days.

The first stage merges into the second, icteric, or toxic stage which lasts until the twelfth or thirteenth day. By this time the leptospirae have usually disappeared from the blood but can be found in increasing numbers in the urine. Immune bodies appear during this stage. The symptoms of the first stage decrease in intensity. Icterus and hemorrhagic phenomena consisting of epistaxes, hemoptyses, hematemeses, purpura and blood in the stools reach their greatest intensity. General weakness, nervous symptoms and signs of cardiac weakness which have their onset during the middle or end of the first stage become most marked. It should be stressed that icterus

occurs only in about one half of the cases. The temperature falls by lysis. Renal changes manifested by albuminuria, casts, red and white cells in the urine, oliguria or even anuria and a rising nonprotein nitrogen may be present according to the severity of the case. When death occurs it usually does so during the second stage due to toxemia, cardiac or renal insufficiency or a combination of these conditions.

In the third or convalescent stage organisms are not present in the blood but are in the urine. They have been demonstrated in the urine as long as seven or eight weeks after the onset of the disease. Antibodies develop fully during this period. Symptoms gradually subside and moderate to marked anemia and emaciation may then become apparent. Convalescence may be prolonged for several months. A second or "after fever," lasting from four to 20 days and occurring in 25 to 75 per cent of the cases, starts usually during the third week of the disease. The after fever is, in most cases, unassociated with other symptoms. The temperature may, however, be above that of the first stage.[2g] It may recur three or four times in the same patient. Leptospirae have not been demonstrated in the blood during the after fever.

Walch-Sorgdrager [17] emphasized the meningeal involvement occurring in the disease. Meningismus or meningitis may occur during the course of the more or less classical form of the disease or as a relatively isolated syndrome. Changes in the spinal fluid, such as increased protein content and pleocytosis, may occur in the typical cases of leptospiral infection without clinically demonstrable evidence of meningeal irritation, as well as in those cases with clinical meningitis. Leptospirae occasionally are found in the spinal fluid and may remain there for a longer period than they usually are present in the blood.[18] Mortensen [19] described a case complicated by meningitis and a complete paralysis of the lower extremities. He was able to collect three similar cases from the literature. He emphasized the fact that there may also be a parenchymal involvement of the nervous system in Weil's disease.

There may be an associated iritis or iridocyclitis which occurs in 10 to 44 per cent of the cases. This complication may appear between the sixteenth and forty-second day and may be associated with the after fever. Skin eruptions occur in 10 to 36 per cent of the cases. The rash may be morbilliform or scarlatiniform; may be large patches or maculopapules; may be erythematous, urticarial or hemorrhagic.[17]

The leptospirae have been found in practically every organ of the body.[2e] The predominant pathological finding aside from the necrosis of the liver cells and nephritis, is hemorrhage due to capillary damage.[20] This is thought to be due to a local toxic effect upon the walls of the vessels. The organs are usually deeply bile stained.

The liver is normal in size or slightly enlarged. Of fairly common occurrence are the proliferation of hepatic cells and traces of bile stasis in the center of the liver lobule. The hepatic cells show active division, the nuclei are swollen and there may be two or three nuclei in some of the cells. In

some cases there may be focal necroses within the liver. Two factors probably play a part in the production of jaundice: one, the swelling of the cells and accompanying edema which may produce obstruction of the bile canaliculi, and two, the deleterious effect upon the liver cells by the leptospiral "toxin." The bile stasis is usually found in moderate degree in the central portion of the liver lobule and not in the periphery of the lobule or in the interlobular or larger ducts.

The kidneys are often enlarged and there may be swelling and more or less necrosis of the epithelium of the convoluted tubules. There may also be infiltration into the interstitial tissues chiefly of lymphocytes with some polymorphonuclear cells and eosinophiles. Small hemorrhages throughout may be noted.

The muscles most severely involved are those of the calf; others may also be affected. Macroscopically, punctate hemorrhages may be seen. Microscopically, the process characteristically selects parts of isolated fibers. With more extensive involvement adjacent fibers or even a whole field may be concerned. The pathological process consists of vacuolation, swelling, loss of striations, hyalinization and infiltration of the fibers with macrophages, polymorphonuclear and plasma cells. The substance of the fiber may be broken up into large lumps of hyaline material.

Kaneko and Okuda [2e] studied the distribution of the leptospirae within the body. They found that early in the disease the organism is located extracellularly. With the progress of the disease and the development of immune bodies, the leptospirae tend to become more frequently enclosed within the cells and to disappear from organs other than the kidney. In the kidney they are found, early in the disease, in the trabeculae, tissue spaces and interstitial tissues; later, in the tubules.

Since the organisms are present in the blood during the first week and occasionally as late as the ninth day, they may be demonstrated there by dark-field examination or guinea-pig inoculation. Demonstration of the leptospirae in a dark-field preparation of blood is rather difficult. This is probably best accomplished by centrifuging the blood at low speeds and examining the plasma.[6] Inada [2g] stated that spirochetes appear in small numbers in the urine during the first stage. During this stage the agglutination reaction is absent or weakly positive. Leptospirae are more easily found in the urine during the second stage and become most numerous at about the thirteenth to the fifteenth day. The agglutination reaction rises from negative to weakly positive (1:100) to highly positive (1:100,000) by the fourteenth or fifteenth day of the illness. This reaction remains highly positive for about seven weeks and then slowly falls to 1:900 to 1:300 where it may remain for several years.[11]

In order to inoculate guinea-pigs 3 to 5 c.c. of blood, 5 c.c. of spinal fluid or the sediment from 40 to 60 c.c. of freshly voided urine suspended in 5 c.c. of normal saline solution are used. After inoculation of the animal intra-

peritoneally there is an incubation period of about six days after which there is a sharp rise in temperature and jaundice occurs. This is followed in about 24 hours by collapse and death. At autopsy jaundice of the skin and internal organs is present. There are petechial hemorrhages in the skin, muscles, peritoneum, kidneys and in the gastrointestinal mucosa. There are multiple, small, sharply defined hemorrhages in the lungs, particularly in the lateral portions of the lower lobes. These hemorrhages have a rather characteristic "butterfly" distribution. There may be large hemorrhages in the adrenals. The leptospirae may be demonstrated in dark-field preparations of scrapings from the liver or kidney or by Levaditi stains of permanent sections of these organs. They may also be seen by dark-field examination of the heart blood.

Syverton et al.[21] commented upon the fact that Weil's disease was diagnosed infrequently in this country despite the wide-spread occurrence of the organism in rats. Since the leptospirae may be of low virulence they recommended that inoculated guinea-pigs be killed, if they do not die by the twelfth day, and that further guinea-pigs be inoculated with blood and kidney of the initially inoculated animals. Three such passages should be carried out before a negative report is made.

Case Reports

Case 1. L. P., a 51-year-old colored woman, was admitted on October 4, 1939 complaining of chills, fever and sore throat. She was a known hypertensive who had had shortness of breath for several years. Eleven days prior to admission she became suddenly ill with chills, sore throat and fever. She had a slight dry cough and generalized and abdominal aching pains. She continued to have chills and fever until admission. Four days before admission she became disoriented and jaundice was noticed.

On admission her temperature was 101° F., pulse and respiratory rates were 90 and 28 per minute respectively. The blood pressure was 130 mm. of Hg systolic and 90 diastolic. She was an obese colored female in a deep stupor. Breathing was irregular and there were periods of apnea. She was markedly jaundiced. Uremic frost was present over the face, ears and neck. There were no eruptions and there was no conjunctivitis. There was generalized hyperesthesia. The remainder of the physical examination was negative.

The urine contained one plus albumin, two plus bile, numerous clumped white cells, and occasional casts. The examination of the blood revealed 5.9 million red and 27,600 white cells per cubic millimeter with a hemoglobin content of 11 grams. There was a slight shift to the left in the differential count. The icterus index was 100 and the Van den Bergh gave a prompt direct reaction with 2.5 mg. bilirubin per 100 c.c. The blood cholesterol was 210 mg. per 100 c.c. The nonprotein nitrogen was 162 mg. and later rose to 261 mg. per 100 c.c. of blood. The stool contained bile pigments and a small quantity of blood as measured by the benzidine reaction. Blood culture was negative. *Escherichia coli* was cultured from the urine.

The patient gradually sank more deeply into coma. Her temperature ranged between 101° and 104° F. In spite of supportive therapy in the form of hypertonic glucose and intravenous saline solution she died on the fourth hospital day.

Permission for autopsy was granted and, while the necropsy was being performed, nine hours after death, Weil's disease was suggested as a cause of this patient's hitherto obscure illness. Accordingly, blood was obtained post-mortem and sent to

the National Institute of Health where an agglutination reaction against *L. icterohaemorrhagica* was carried out with "positive results."

At autopsy the organs showed marked jaundice. There was central atrophy of the liver. Due to the obesity and jaundice there was too much postmortem change to be sure of focal necroses within the liver. An acute glomerular nephritis was present with proliferation of the glomerular epithelium, colloid degeneration of the tubular epithelium and tubular hemorrhages. Capillary hemorrhages in the brain and stomach were also present. The spleen presented the usual picture seen in patients with the sickle cell trait.

Case 2. P. E., a 48-year-old colored female, was admitted August 28, 1940 complaining of "something moving" in her stomach. Two months prior to admission she began to have severe, intermittent, aching pains in the right upper quadrant of her abdomen. These pains recurred two or three times each week. Two weeks before entry her stools became light yellow in color and her urine became dark. Nine days prior to admission she experienced two shaking chills followed by fever. At the same time the abdominal pains became more severe and frequent. Shortly thereafter she began to bleed from the mouth and the vagina and she noted urinary frequency and itching of the skin. The day before admission she was told that her eyeballs were yellow.

On admission her temperature was 100° F., pulse and respiratory rates were 96 and 24 per minute respectively. The blood pressure was 135 mm. of Hg systolic and 80 diastolic. She was well developed and fairly well nourished. She was quite drowsy, responded poorly to questions, but coöperated fairly well. The sclerae were deeply jaundiced. There were numerous large and small fresh retinal hemorrhages and a large sausage-shaped rupture of the choroid in the right eye. The left eye was negative except for moderate arteriosclerotic changes in the vessels. The lungs were clear. The heart was slightly enlarged and there was a systolic murmur at the apex. The second aortic sound was somewhat ringing. There was moderate rigidity of the right upper quadrant of the abdomen but no definite tenderness. No organs or masses were felt in the abdomen. The remainder of the examination was negative.

At the time of admission the urine contained one plus albumin, 4 to 5 leukocytes per high power field and an occasional red cell. Bile was present in the urine in large quantities on admission and became negative in two weeks. Urobilin was not increased on admission but appeared in large quantities one week later and gradually returned to normal in four weeks. Beta hemolytic streptococci and *Staphylococcus albus* were cultured from the urine. The stool contained bile pigments and occult blood on admission; the blood soon disappeared. Examination of the blood revealed 4.1 million red cells and 20,000 white cells per cubic millimeter and a hemoglobin content of 14.5 grams. The differential was normal except for a slight increase in the immature forms. In two weeks the hemoglobin dropped to 9.2 grams and the white count became normal. The nonprotein nitrogen of the blood was 150 mg. per 100 c.c. on admission and returned to normal one week later. The icterus index was 100 on admission and fell to 10 in five weeks. The Van den Bergh was direct on admission with 21.5 mg. bilirubin which became indirect with a 0.6 mg. bilirubin per 100 c.c. five weeks later. The cholesterol was 230 mg. and the total protein 6.3 grams per 100 c.c. with an albumin-globulin ratio of 2.0/4.3. The Eagle and Wassermann reactions of the blood were positive, but the spinal fluid was negative. A roentgen-ray of the chest revealed a moderately enlarged heart and a slightly dilated aorta. There was also a stringy infiltration at the right base. Gall-bladder series revealed negative shadows in the gall-bladder which were interpreted as cholesterol stones.

Two days after admission two guinea-pigs were inoculated intraperitoneally; one with blood, and the other with urine from the patient. The guinea-pig which was inoculated with blood remained well. The guinea-pig inoculated with urine died on the

tenth day. Jaundice and small hemorrhages were found throughout the organs and a few leptospirae were found by dark-field examination. A third animal was inoculated with urine from the second guinea-pig. This animal died on the fifth day with marked jaundice, many hemorrhages and numerous organisms.

Blood sent to the National Institute of Health during the first week was found to agglutinate *L. icterohaemorrhagica* to a titer of 1:10,000. Two weeks later a second specimen was found to agglutinate the organism to a titer of 1:100,000. At the time of discharge, Dr. T. G. Ward at the Johns Hopkins School of Hygiene and Public Health found agglutination to occur to a titer of 1:60,000, and after the syphilitic reagin was adsorbed, agglutination occurred to the same dilution.

During the first week in the hospital, the patient was quite drowsy and had a low grade fever. Treatment was directed toward improving kidney function and the patient responded quite well. Jaundice disappeared slowly as did her abdominal symptoms. Her course was complicated by a urinary tract infection and by mild cardiac failure; both responded satisfactorily to treatment. She was discharged October 30, 1940 much improved.

Case 3. S. E., a 54-year-old white man, entered the hospital December 20, 1940 complaining of malaise. Previously he had been well except for typhoid fever which he had had in 1904. He was a poultry dresser and had been occupied as such since the age of fifteen. There were numerous rats about the place in which he was working. He was taken ill rather suddenly 10 days before admission with cough and a small amount of sputum. For a few days after the onset he had rather sharp pains in his calves and thighs as well as a headache. Four or five days prior to admission, jaundice was noticed for the first time. During the past week he had had frequent bouts of nausea and vomiting and several epistaxes.

On admission his temperature was 102° F., pulse and respiratory rates were 116 and 24 per minute respectively. Blood pressure was 105 mm. of Hg systolic and 65 diastolic. He was a thin white male, strikingly jaundiced, who did not appear acutely ill but was somewhat apathetic. Over the trunk, arms and legs, there were numerous slightly raised, erythematous areas about two or three mm. in diameter which faded on pressure. There was no conjunctivitis, glandular enlargement or tenderness in the calves or thighs. There was some dried blood in the nostrils and on the tongue and lips. The lungs were negative except for a few medium dry râles at both bases. The heart was not enlarged but there was a very short pre-systolic rumble at the apex. The abdomen was easily palpated and both kidneys were felt. The liver was questionably palpable two fingers'-breadth below the costal margin. The remainder of the physical examination was negative.

The urine was negative for albumin, cells and casts. Bile and urobilin, which were present in large quantities at the time of admission, gradually disappeared during his hospital stay. The stool contained bile pigments but no blood. Examination of the blood revealed 3.41 million red cells, 16,400 white cells per cubic millimeter and a hemoglobin content of 12 grams. The nonprotein nitrogen was 32 mg.; cholesterol 220 mg. and the total proteins, 5 grams per 100 c.c. of blood. The albumin-globulin ratio was 3.1/1.9. Prothrombin time three days after admission was 78 per cent of normal. The icterus index, which on admission was well over 100, slowly became normal before discharge. The Van den Bergh gave a prompt direct reaction on admission with a bilirubin content of 23.5 mg. per 100 c.c. This soon became indirect and subsequently returned to normal values. The Eagle reaction was negative.

Guinea-pigs inoculated with blood were negative. Of two inoculated with urine, one died 13 days later with mild jaundice and a moderate number of hemorrhages in the lungs and intestines. Dr. T. G. Ward was able to isolate leptospirae from the heart blood of the other guinea-pig which had been inoculated with urine. Serum sent to the National Institute of Health on December 30, 1940 agglutinated *L. icterohaemor-*

rhagica in a dilution of 1 : 100,000 and *L. canicola* 1 : 1,000. This was repeated, using *L. icterohaemorrhagica* only, with the same results.

During the first week the patient's temperature ranged between 100° and 102° F. The rash spread for the first two days and then gradually disappeared. Four days after admission, a parotitis developed on the right side which subsided in about six days. A moderate anemia developed and the red count fell as low as 2.4 million cells per cubic millimeter. Otherwise, his course was uneventful except for a low-grade fever which he had for most of the remainder of his stay in the hospital.

Case 4. E. P., a 58-year-old colored man, entered the hospital March 1, 1941 complaining of a "cold" and pain in his chest. He had had "chills and fever" as a young man while in Georgia. In 1922 he had a post-pneumonic empyema for which a thoracotomy was performed. About one week before admission he began to have a cough and soon thereafter he had a few shaking chills. He became increasingly weak and began to suffer from vague pains in his legs, abdomen and chest. He stated that his legs were somewhat tender at that time. There were numerous rats about the place in which he lived and he frequently found them eating the food he had intended to eat.

On admission his temperature was 101.8° F., pulse and respiratory rates were 90 and 22 per minute respectively. The blood pressure was 102 mm. of Hg systolic and 90 diastolic. He was a fairly well nourished colored male who was quite drowsy and responded poorly and vaguely to questions. The skin was dry and the conjunctivae were icteric but not injected. There was no tenderness of the muscles of the calves or thighs. There was a slight lag of the right hemithorax with an old thoracotomy scar on that side. The right base did not descend well and there were a few fine râles at the angle of the right scapula. The heart was not enlarged and there were no murmurs over the precordium. The liver was not felt but the spleen was firm and descended about three centimeters below the costal margin. The remainder of the physical examination was negative.

The urine contained a small amount of albumin, moderate amounts of bile and urobilin and occasional red and white blood cells. The urine became clear about three weeks after admission. The stool contained bile pigments but no blood. Examination of the blood revealed 5.33 million red cells, 9,160 white cells per cubic millimeter and a hemoglobin content of 13 grams. The nonprotein nitrogen was 50 mg.; the total proteins were 6.0 grams per 100 c.c. of blood. The nonprotein nitrogen fell to 30 mg. per 100 c.c. in a few days. The icterus index, which on admission was 100, gradually became normal. The Van den Bergh gave a biphasic reaction with a bilirubin content of 3 mg. per 100 c.c. of blood at the time of admission. The Eagle reaction was negative. The cerebrospinal fluid was negative. Serum sent to the National Institute of Health on March 11 agglutinated *L. icterohaemorrhagica* to a dilution of 1 : 10,000; on March 18, the reaction was positive to a titer of 1 : 100,000. Guinea-pigs inoculated with urine did not die and we were unable to obtain the organism even after further transference to other guinea-pigs.

The patient's temperature ranged from 101° to 102° F. for two days. After that it remained at about 100° F. for two weeks before returning to normal. He soon began to gain slowly in strength. A slight anemia of 3.87 million red cells per cubic millimeter developed during the second week of his hospitalization.

Case 5. W. T., a 28-year-old colored man, entered the hospital April 28, 1941 complaining of jaundice. Ten days before admission he suddenly became ill with headache, fever and aching pains in his back and arms. These symptoms continued for five days, then gradually subsided. Following this he became very weak. He noticed that his urine was dark, and, three days prior to admission, jaundice was first called to his attention.

He worked in a restaurant but knew of no rats there. Near his home a slum clearance program was in progress and, while the buildings were being torn down, he noticed many more rats than usual in his back yard.

On admission his temperature was 99.6° F., pulse and respiratory rates were 60 and 22 per minute respectively. The blood pressure was 110 mm. of Hg systolic and 70 diastolic. He was a well developed colored man who appeared to have lost a little weight. Although coöperative, he was somewhat listless and drowsy. There was marked jaundice of the sclerae. The liver lay two fingers'-breadth below the costal margin and the lower poles of both kidneys were readily palpable. The physical examination was otherwise negative.

The urine contained moderate amounts of bile and urobilin but no albumin, cells or casts. The bile and urobilin disappeared by the time of discharge. The stool contained bile pigments but no blood. Examination of the blood revealed 4.01 million red cells, 13,100 white cells per cubic millimeter and a hemoglobin content of 11.8 grams. No anemia developed during his stay in the hospital. The nonprotein nitrogen was 23 mg. per 100 c.c. of blood. The icterus index was 50 at the time of admission and reached 15 before discharge. The Van den Bergh gave a biphasic reaction with a bilirubin content of 7.1 mg. on admission. The Eagle reaction was negative. Serum sent to the National Institute of Health on April 28 agglutinated *L. icterohaemorrhagica* to a dilution of 1 : 1,000 while that sent May 12 agglutinated the organisms to a titer of 1 : 10,000. Urine sediment was injected into guinea-pigs on May 1. One week later the animals died with jaundice and pulmonary hemorrhages. Numerous leptospirae were seen by dark-field examination of the emulsified kidney.

His stay in the hospital was an uneventful one, during which he rapidly regained strength and was discharged May 12, 1941.

Case 6. G. Y., a 42-year-old white man, was admitted to the hospital May 13, 1941 complaining of nausea and vomiting. He had been observed in a neurologic clinic for 16 years because of idiopathic epilepsy. He had had a slight "cold" with cough and nasal discharge for nine days prior to admission. Four days before entry, he had a sudden severe shaking chill followed by feverishness and malaise. Next day he developed an aching pain in his lower back which became severe. His cough increased and nausea and vomiting developed to such an extent that he was unable to retain anything but small amounts of liquids. There had been a moderate epistaxis on the day prior to admission. He was a sewer worker.

On admission his temperature was 102.6° F., pulse and respiratory rates were 134 and 20 respectively. The blood pressure was 108 mm. of Hg systolic and 80 diastolic. He was a thin, acutely but moderately ill white male who was somewhat drowsy and slightly confused. The conjunctivae were injected but there was no icterus. There were a few sonorous râles scattered throughout the chest. The spleen and liver were not felt. The physical examination was otherwise negative.

The urine contained a small amount of albumin and occasional red and white blood cells. Bile and urobilin appeared a few days later. Examination of the blood revealed 5.1 million red cells, 7,800 white cells per cubic millimeter and a hemoglobin content of 14.6 grams. The white cells rose to 15,700 two days later. At the time of admission the nonprotein nitrogen was 50 mg. per 100 c.c. of blood; on May 19 it was 100 mg. per 100 c.c. It fell to 38 mg. on May 21 and then rose gradually to 120 mg. on May 29, only to fall again to normal before discharge. The icterus index rose from 30, three days after admission, to 100 three days later and became normal by the time of discharge.

Dark-field examination of the blood on May 17 revealed a moderate number of *L. icterohaemorrhagicae*. A guinea-pig inoculated with urine on May 29 died 16 days later with jaundice and hemorrhages in the lungs. Numerous organisms were seen by

dark-field in the emulsified kidney. Serum sent to the National Institute of Health agglutinated *L. icterohaemorrhagica* to a titer of 1 : 10,000 on May 25 and to a titer of 1 : 100,000 on May 28.

The patient's temperature ranged irregularly up to 103° F. during the first week in the hospital. Following this, it became normal for five days and then suddenly rose to 103°–104° F. where it remained for two days. The temperature subsequently returned to normal for the duration of his hospital stay. Jaundice first appeared three days after entry and became very deep before it finally subsided. A few small erythematous maculo-papules were visible on the abdomen for two days one week after admission. At the time of the "after fever" no change in the patient's condition other than increased drowsiness and a rising nonprotein nitrogen could be observed. Spinal fluid examination was negative. The patient was critically ill during the early part of his illness but after the second rise in temperature, his recovery was a steady one. A mild anemia of 11 grams of hemoglobin has developed during convalescence.

It is probable that the diagnosis of Weil's disease would be made more frequently in this country if this illness were considered more often in the differential diagnosis of jaundice of unknown etiology or of any obscure illness which may have as its features muscle pains, conjunctivitis and fever of rather sudden onset. The final diagnosis rests upon the results of the laboratory procedures. One should bear in mind, as a means of establishing the diagnosis, the agglutination reactions and guinea-pig inoculations with blood and urine. The history of contact with the urine of wild rats, through occupation or in some other manner, is a valuable aid. Sudden onset of a febrile illness with or without chill and later jaundice, with muscular pains, gastrointestinal disturbances, redness of the conjunctivae, albuminuria, and epistaxes, should suggest Weil's disease. Jaundice, occurring during an acute illness, associated with hepatomegaly but without splenomegaly or general glandular enlargement should also suggest this disease. Furthermore, in any case of serous meningitis, one should consider this disease very carefully.

The disease may vary from an extremely mild one without jaundice and resembling influenza to a very severe prostrating illness with a fatal outcome. Abrupt onset, leukocytosis and albuminuria are important points in differentiating this disease from catarrhal jaundice. Nephritis occurs in 89 per cent of those cases with jaundice and in 75 per cent of those without jaundice.[17] The diagnosis of the disease without jaundice is extremely difficult. Muscular pains, albuminuria, conjunctivitis and leukocytosis in addition to a history which may suggest a contact with the urine of rats may be helpful. Probably one of the most noteworthy features of the disease is the striking apathy of the patients. This was an outstanding characteristic of four of our patients. One of our cases, admitted with jaundice and azotemia, was thought to be suffering from acute yellow atrophy. This would suggest that any similar case without a known etiological agent should be thoroughly investigated for the possibility of Weil's disease.

The prognosis is influenced by age, presence or absence of jaundice, cardiac function and the presence or absence of uremia. As the age of the

patient increases, the prognosis becomes proportionately more grave. Walch-Sorgdrager [17] found that the fatality rate in patients aged 10 to 40 was 10 per cent, from 40 to 60 it was 24 per cent, and in those cases over 60 it was 60 per cent. The case fatality rate for those cases without jaundice is negligible.[6, 17] The case fatality for all ages varies from 16 to 32 per cent in those cases with jaundice. In the United States, Jeghers, Houghton and Foley [20] found the case fatality rate to be 41 per cent. Uremia has an unfavorable influence on the prognosis particularly if oliguria or anuria is present. An increase in urinary output with a fall in the nonprotein nitrogen are favorable signs, although the patient may still die of cholemia or cardiovascular collapse.

An active immunity may be produced by the injection of killed organisms. Inada et al.[2d] used immunized horse and convalescent human serum and reduced the case fatality rate from 30.6 to 17.3 per cent. More recently, however, Walch-Sorgdrager concluded, "although the evidence as a whole does not conclusively demonstrate that serum exerts any specific action upon the pathogenic organisms it seems clear that it has a beneficial effect when administered within four days of the onset of the disease." In light of the recent work on treatment of diseases of the liver with a high carbohydrate low fat diet, it is probable that such a diet would prove useful in the treatment of those cases with jaundice.

Summary and Conclusions

Six cases of Weil's disease occurring within a period of 20 months are reported. Case 1 was that of a 51-year-old colored female, extremely jaundiced, who died in uremia. The cause of the illness was obscure but at autopsy, the history of uremia and the presence of jaundice and petechial hemorrhages suggested the correct diagnosis which was confirmed by the agglutination reaction. Case 2 bore a marked similarity to the first case, and because of this fact the necessary steps in confirming the diagnosis were undertaken. Case 3 might have been diagnosed as catarrhal jaundice had we not had experience with the two previous cases. Case 4 was somewhat atypical because of the large spleen. This, however, was probably due to a malarial infection which he almost surely had had in the past. Cases 5 and 6 were more or less typical.

Goldberg and Davens [22] reported two cases in children occurring at the Harriet Lane Home. These eight cases, which occurred within a short period of time in Baltimore, should help to illustrate the widespread incidence of this disease. It is our feeling that the diagnosis of Weil's disease would be made more frequently if the agglutination reaction were performed in cases of jaundice of obscure etiology; in those cases presenting some of the usual features of the disease as described; and in atypical forms of meningitis.

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THE DIAGNOSIS AND MANAGEMENT OF BRUCELLOSIS *

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THE past decade has witnessed a remarkable advance in our knowledge of the incidence of brucellosis. The author's prediction,[1] in 1930, that brucellosis would probably soon become recognized as a public health problem of major proportions, was based upon the discovery of 90 cases of the disease in and about Dayton during a period of 18 months. Prior to this investigation the disease was not known to be prevalent in this area. The results of other surveys conducted during recent years in widely separated parts of the United States provide unmistakable evidence of the widespread distribution of brucellosis and leave little doubt that this disease is a common and a frequently unrecognized source of disabling illness.

That milk-borne brucellosis may be practically eliminated from a community by the adoption of a universal pasteurization ordinance is demonstrated by the Dayton experience. During the four years prior to the passage of such an ordinance in Dayton, in 1931, 196 cases of brucellosis were encountered. All but one of the 52 cases studied by the author during the past decade have occurred in persons who consumed raw milk or other unpasteurized dairy products elsewhere, usually while vacationing, prior to the onset of illness. The single exception was an employe of a local dairy who drank milk before it was pasteurized.

Prior to 1926, the sporadic cases which were encountered were regarded as clinical curiosities. Most of these were related to endemic foci of goat infection in Texas, New Mexico, and Arizona. From 1927 to 1930, the number of recorded cases rose from 217 to 1385. During 1929, cases of brucellosis were encountered in every state of the Union. In 1940, 3358 cases were officially reported to the U. S. Public Health Service by State Health Departments.[2] It is undoubtedly true that the number of cases actually occurring is much larger than that reported.

Among urban populations, the chief mode of transmission of the disease is by the ingestion of raw milk and unpasteurized dairy products derived from cattle infected with *Brucella abortus*. Of the 248 patients with brucellosis studied personally by the writer, the ingestion of raw milk or unpasteurized dairy products containing the organism of contagious abortion of cattle was demonstrated to be the source of infection in the great majority of instances. Direct dermal transmission may be the mode of infection among dairymen, veterinarians or slaughter house workers. Hardy expresses the

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belief that direct contact with infected cattle and hogs has been responsible for a great number of cases of brucellosis occurring in Iowa. Hardy [3] has demonstrated by animal experiments that the skin may act as the portal of entry of the organism. Morales-Otero,[4] of Puerto Rico, has reproduced the disease in human volunteers by inoculations through abraded skin. It is apparent, therefore, that there are two important sources of infection for man: commonly by the ingestion of raw milk or unpasteurized dairy products containing *Brucella*, or less frequently as the result of direct contact with infected fresh animal tissues or discharges. There is no definite evidence of man-to-man transmission of the disease.

Clinical Manifestations in Man

Because brucellosis presents many symptoms and signs common to typhoid fever, malaria, tuberculosis and influenza, it is frequently confused with these diseases. Many physicians have arrived at a tardy diagnosis of brucellosis only after repeated negative Widal reactions, the failure to demonstrate the malarial plasmodium, and the inability to elicit physical signs or roentgen-ray evidence of tuberculosis. Less often, the disease has been confused with acute rheumatic fever, subacute bacterial endocarditis, bronchitis, pyelitis, appendicitis, cholecystitis, or tularemia.

Symptomatology

As knowledge of the clinical manifestations of brucellosis has advanced, particularly during the past decade, it has become more and more apparent that the older textbook descriptions of the symptomatology of the disease were based largely upon experiences with brucellosis of goat origin. The classical clinical picture of a disease characterized by an undulatory, remittent, or intermittent fever, drenching sweats, chills, headache, backache, muscular and joint pains, weakness, loss of weight, possibly a palpable spleen, an infrequent skin eruption, leukopenia with lymphocytosis, and anemia, pertains chiefly to the severe acute forms of the disease. In a high proportion of cases, the disease pursues a relatively mild, prolonged course, extending over many months or years. The early descriptions by Hughes [5] and Craig [6] included many such cases. Alice Evans and others have more recently directed particular attention to the common chronic ambulatory form of brucellosis, in which the patient, whose spirits are already depressed by continued ill health, is often given further discouragement when a diagnosis of neurasthenia is made. Many "neurasthenics," whose chief complaints were exhaustion, insomnia, irritability, and a variety of aches and pains have been found to be victims of chronic brucellosis.

Since the symptomatology of the acute and the chronic forms of brucellosis varies so greatly, these two manifestations will be considered separately.

Acute Brucellosis

The incubation period has been found to vary from five days to longer than one month. In accidental laboratory infections the incubation period has varied from 10 to 20 days. The prodrome is not unlike that of any general infection, with a gradual onset, although in occasional cases the disease is initiated with a sharp chill and rapid elevation of temperature to 103–105° F. (39.4–40.6° C.). A sense of tiredness and weakness, loss of appetite, constipation, headache and backache are common early symptoms. Usually, the patient becomes gradually aware of an afternoon or evening rise in temperature, associated with chills or chilly sensations, nocturnal perspiration and weakness. The patient often feels quite well during the morning hours, particularly in the early stages of the infection. As the temperature rises, during the afternoon or evening, the symptoms gradually return and increase in severity. The nocturnal exacerbations of fever occasionally reach great heights (106–107° F.; 41.1–41.7° C.). There is often a remarkable disparity between the subjective sense of fever and the height of the fever as registered by the clinical thermometer; in many instances the patient does not complain of fever, nor does he present a febrile appearance, but the physician finds, to his surprise, a fever of 101–103° F. (38.3–39.4° C.). As the fever abates, chills and sweating occur. If defervescence is rapid, the perspiration is more likely to be of a drenching character. In such cases, the sweats, which literally saturate the night clothing and bedding, are one of the most impressive features of the disease. The perspiration often has a peculiar sweetish, fetid odor. The chills may be severe enough to be regarded as true rigors in about one-third of the acute cases.[1, 7, 8] Many patients experience only mild chilly sensations, while in about one-fourth of cases chilliness is absent.

Arthralgia and muscular pains are prominent features of the acute form of the disease in approximately one-half of the cases. The joint pains may be more pronounced during the onset or they may persist throughout the course of illness. The myalgia may be accompanied by a feeling of "stiffness" not unlike the muscular soreness which follows vigorous exercise. Hydrarthrosis and transient periarticular swelling have been observed occasionally. Green and Freyberg[9] investigated the incidence of brucellosis in patients with rheumatic disease; they found that while *temporary* nonpurulent joint inflammation does occur, chronic arthritis rarely, if ever, occurs as a complication of brucellosis. We have encountered no instances of permanent joint impairment. Suppurative osteomyelitis as a complication of brucellosis has been described with increasing frequency during the past few years.[10–18] In most of the reported cases the vertebrae, particularly in the lumbar region, were attacked. In some instances other bones, such as the humerus, femur, skull and ribs, were affected. Feldman and Olson[19, 20] found similar examples of *Brucella* spondylitis in 24 hogs, an average occurrence of one in every 6000 swine slaughtered.

Marked restlessness and insomnia usually accompany the nocturnal febrile exacerbations. Delirium occurs in some cases in which the fever reaches great heights. Regional *Brucella* localizations in the brain, spinal cord or meninges may occur during the acute phase of the disease and produce symptoms and signs of encephalitis, myelitis or meningitis; such complications are, however, more commonly observed as delayed manifestations of brucellosis. The meningeal involvement predominates, and the development of encephalitis or myelitis, or both, is usually secondary to the meningitis. The involvement of the central nervous system may produce the first and only symptoms of the disease. The symptomatology varies greatly, depending upon the extent of meningeal invasion and the presence of additional complications involving the brain, spinal cord or peripheral nerves. In a patient with brucellosis, the development of such symptoms and signs as severe headache, vertigo, diplopia, nuchal rigidity, aphasia, psychic disturbances and various forms of paralysis which are often evanescent, calls for examination of the cerebrospinal fluid. Characteristically, the spinal fluid will be under increased pressure and will show pleocytosis, increase of albumin and a decrease of globulin and sugar. Since the ultimate diagnosis during life depends upon the isolation and identification of *Brucella* from the spinal fluid, a particularly diligent effort should be made to recover the organism by culture and by guinea pig inoculation. DeJong [21] has recorded 11 verified cases of *Brucella* meningitis or meningoencephalitis in which the organism was recovered from the spinal fluid by culture or by guinea pig inoculation.

A growing body of evidence indicates that ocular complications of brucellosis are not uncommon. We have encountered at least eight instances of ocular disease occurring as a manifestation of brucellosis. Green [22] has found that the cornea, the uveal tract, the retina, the optic nerve and the external ocular muscles are vulnerable to attack. In addition to four cases (corneal ulcer, retinitis, optic neuritis and central retinochoroiditis) encountered in his own practice, Green describes 27 additional cases reported in the literature. Rutherford [23] found papilledema in three of 63 cases of brucellosis examined ophthalmoscopically. Rutherford suggests inclusion of brucellosis in the differential diagnosis in cases of papilledema in which the symptomatology is indefinite. Ruedemann [24] states that brucellosis is responsible for uveitis much more commonly than is generally believed; he found brucellosis to be responsible for chronic uveitis in seven of 125 patients with uveal tract disease.

The matutinal remissions or intermissions and the nocturnal exacerbations of fever may last from one week to many months. The inadequate name "undulant fever" refers to recurring relapses of fever following afebrile intermissions. Such febrile relapses are the exception rather than the rule; most patients experience but one febrile period, lasting from a few days to several months, and finally reaching the normal level by lysis.

The essential gastrointestinal complaints are anorexia and constipation.

The degree of constipation appears often to parallel the severity of the infection. Diarrhea is of rare occurrence. Nausea and vomiting may occur in the more severe cases. Abdominal pain is a not infrequent feature of the disease during its early manifestations. Among 125 cases studied by Hardy, abdominal pain occurred in 40; in 10 it was the major complaint. Simpson found abdominal pain to be the chief complaint in 16 of 142 patients with brucellosis. The occurrence of abdominal pain has often led to appendicectomy in patients with unsuspected brucellosis, the correct diagnosis having been made only after the persistence of febrile symptoms stimulated a further search for the cause. As in typhoid fever, the gall-bladder may become a focus of *Brucella* infection. *Brucella* has been recovered from the excised gall-bladder and from the bile following duodenal drainage in patients with symptoms of cholecystitis.[25, 26, 27]

Symptoms referable to the respiratory tract may be an outstanding feature of the disease in certain instances. Cough, associated with mucoid or muco-purulent sputum production, is not infrequent during the first few weeks of illness, and may persist for months. Recent reports [28-32] provide convincing evidence that pulmonary lesions of brucellosis are of frequent occurrence and are often detectable by roentgenographic examination, even in the absence of distinctive physical signs of pneumonia. The lesions most often encountered on roentgen-ray examination are peribronchial infiltrations, hilar infiltrations, and scattered discrete or confluent patchy pneumonic areas. The pulmonary manifestations of brucellosis should be regarded as hematogenous lobular pneumonia rather than true bronchopneumonia. Without doubt, pulmonary lesions occur much more commonly than is generally realized. Serial roentgenographic studies will often provide an explanation for vague respiratory symptoms.

The most serious cardiovascular complication has been the occasional occurrence of vegetative endocarditis. Smith and Curtis [33] found reports of nine cases of *Brucella* endocarditis confirmed by postmortem examination, to which they added a similar case. In most instances the vegetations occurred on mitral or aortic valves previously damaged by rheumatic fever.

The name commonly applied to brucellosis of cattle, "infectious abortion," is derived from the well known predilection of the causative organism for the genital tract. There is strong evidence that the same regional localization sometimes occurs in human beings. Painful swelling of the testes has been described frequently. Acute epididymitis, orchitis, prostatitis and seminal vesiculitis may be early manifestations of the disease. Simpson [1] recovered *Brucella abortus* from a draining sinus tract which extended from the globus major of the epididymis through the scrotal wall.

There appears to be little doubt that brucellosis is at least an occasional cause of abortion in women who live on farms where they have direct contact with infected animals, or in women who consume raw milk or unpasteurized dairy products. There are reports [34-37] of human abortion in which

the history and serologic findings provide strong circumstantial evidence of the etiologic rôle of *Brucella*. In a study of 565 cases of brucellosis, Calder [38] found a history of one or more miscarriages in 32 per cent of the married women; a history of one miscarriage followed by sterility was common; a few women reported as many as five or six abortions. More direct evidence has been provided by Carpenter and Boak [39] who recovered *Brucella abortus* from the tissues of a human fetus which was aborted at the end of the fourth month of gestation. Kristensen [40] isolated the *abortus* variety of the organism from the exudate which covered the uterine site of the placenta of a seven-month fetus. Frei [41] isolated *Brucella* from the vaginal discharge of a woman who had aborted 10 days previously.

Loss of weight is an almost constant feature of the acute form of the disease. The greatest loss, often from 10 to 50 pounds, occurs in those patients who experience high fever, drenching sweats and great prostration.

A transient cutaneous eruption, usually papular, macular or maculopapular, is a relatively infrequent finding. The skin lesions may simulate the roseola of typhoid fever.

Chronic Brucellosis

Many physicians feel that the symptoms and signs of acute brucellosis are often sufficiently characteristic to justify such a provisional diagnosis on the basis of clinical findings. In dealing with chronic brucellosis, however, the physician is often faced with a problem which will tax his diagnostic acumen to the utmost. No disease, not excepting syphilis and tuberculosis, is more protean in its manifestations.

Quite naturally, a certain amount of wholesome skepticism has arisen in the minds of some physicians regarding any wide prevalence of chronic brucellosis. Such a feeling of doubt is quite defensible, since one is justified in questioning the validity of some of the diagnostic tests upon which such a diagnosis is often based.

The common and unfortunate employment of the name "undulant fever" has served only to add further difficulties in the recognition of cases of chronic brucellosis. A significant temperature curve, physical signs of disease, and positive agglutination tests and skin tests may be entirely lacking throughout a long period of chronic illness. The recent studies by Evans,[42, 43, 44] Poston,[45] Angle,[46] Scoville,[47] Thames,[48] Calder,[38] Hamman and Wainwright,[49] Harris,[50] Cameron and Wells,[51] Gould and Huddleson,[52] Gersh and Mugrage,[53] and Angle, Algie, Baumgartner and Lunsford [54] leave little doubt that a protracted, relatively mild, partially disabling, often ambulatory, form of brucellosis is widely prevalent and constitutes a major cause of chronic ill health. Only a small proportion of patients with chronic brucellosis, probably less than 10 per cent, have experienced a previous acute febrile illness, compatible with a diagnosis of acute brucellosis. In many cases the patient is not entirely incapacitated for work, but complains chiefly

of weakness and exhaustion, with or without mild fever. Since the commonly employed diagnostic tests are frequently negative in such cases, and since even the most conscientious physician may not find physical abnormalities to account for the patient's complaints, the almost inevitable diagnosis of neurasthenia or psychoneurosis is too often made.

A recitation of all of the symptoms which have been ascribed to chronic brucellosis would serve only to heighten the confusion which as yet surrounds this baffling phase of the disease. In general, it may be stated that the three cardinal features of most cases of chronic brucellosis are weakness, low-grade fever and a lack of objective physical findings. McGinty and Gambrell [55] have listed over 150 different manifestations of chronic brucellosis. Mild degrees of fever may be present for many weeks or months, there may be several months of complete freedom from fever; sudden febrile exacerbations may occur, accompanied by an accentuation of the prevailing symptoms, or by the development of evidence of new regional symptoms affecting the respiratory, cardiovascular, genitourinary, gastrointestinal, skeletal or nervous systems. Pneumonia, endocarditis, orchitis, epididymitis, prostatitis, oöphoritis, cholecystitis, hydrarthrosis, arthritis, spondylitis, osteomyelitis, ocular complications or meningoencephalitis may be associated with the acute form of the disease, but much more commonly appear several months, or even years, after the often indefinite onset of the chronic form of brucellosis. In some instances such delayed evidences of regional *Brucella* localization may appear long after apparent recovery from the acute manifestations of the disease. All students of chronic brucellosis have emphasized the almost universal prominence of symptoms which relate to the central nervous system. In addition to the occasional acute invasion of the meninges, brain and spinal cord by *Brucella*, there is evidence [56] that the endoantigen of *Brucella* organisms circulating in the blood has a toxic action upon the central nervous system. These observations led Evans [42] to state: "These facts challenge the right of a physician to make a diagnosis of neurasthenia—a diagnosis regarded as dishonorable by the patient, and also by his family, his employer and his friends—without considering, among other possibilities, the possibility of chronic brucellosis."

Chronic brucellosis should be suspected in all cases of so-called "fever of unknown origin." There are many reports of the isolation of *Brucella* from the blood, urine, bile or from extirpated tissues in patients who have experienced unexplained, long-continued, low-grade fever for years. Hamman and Wainwright [49] reëxamined 36 such patients; an accurate diagnosis was finally made on 10 of them; three were found to have brucellosis.

Diagnosis

Since it is hazardous to base a diagnosis of brucellosis solely on clinical grounds, recourse must be had to laboratory diagnostic tests. These procedures include (*a*) primary isolation of the causal organism by cultural

methods from blood, spinal fluid, secretions, excretions, or excised tissues; (*b*) indirect recovery of *Brucella* by culture after animal inoculation; (*c*) the agglutination test; (*d*) the intradermal test; and (*e*) the opsonocytophagic reaction.

The only method by which the diagnosis of brucellosis may be completely established is by the *cultivation and identification of the organism.* While cultural technics have improved greatly during the past few years, with a corresponding increase in the number of reported instances of recovery of the organism, the undertaking is often beset with difficulties and requires skill and, above all, patience. The *melitensis* and *suis* varieties of *Brucella* ordinarily grow readily under aerobic conditions, while the much more commonly encountered *abortus* variety requires an atmosphere containing 10 per cent carbon dioxide. The procedure used by Poston[45] with notable success is as follows: 15 c.c. of blood are obtained from each patient by venipuncture and placed in a small flask containing 4 c.c. of sterile 2.5 per cent sodium citrate solution. Four flasks containing 100 c.c. of liver infusion broth of pH 6.8 are each inoculated with 2 c.c. of the citrated blood. The flasks are incubated at 37° C., two in the room atmosphere and two in an atmosphere containing 10 per cent CO_2. After four days' incubation, daily smears of the broth cultures are made and stained by Gram's method. If no organisms are seen in the smears after 10 days' incubation, 5 c.c. of the original culture are transplanted to 100 c.c. of liver infusion broth every three days for two weeks. Original cultures and transplants are incubated for three weeks before they are reported as negative.

The guinea pig is the most suitable laboratory animal for inoculation. Poston inoculates three guinea pigs with blood from each patient; two are injected intraperitoneally with 2 c.c. each of citrated blood; one is inoculated in the groin with 1 c.c. of citrated blood. The animals are observed daily. Beginning two months after inoculation, tests for specific agglutinins and for cutaneous reaction to Huddleson's brucellergin are made at intervals of a few days. When both tests become positive the animals are killed. Animals which remain negative to the agglutination test and to the skin test are killed four and one-half months after inoculation. Liver infusion broth is planted with the guinea pig's blood and with pieces of organs and is subjected to the cultural procedures previously described. The cultures may then be differentiated into *abortus, suis* or *melitensis* varieties by the agglutinin-absorption technic, the bacteriostatic action of dyes, glucose utilization and hydrogen sulphide metabolism.[57, 58, 59]

The most commonly used and the most reliable indicator of *Brucella* infection, in the absence of positive cultures, is the *agglutination test.* This is particularly true in cases of acute brucellosis, in which a high serum agglutinin titer will be found in a great majority of cases. Considerable diagnostic significance may be attributed to a progressive increase in the agglutinin titer upon repeated testing in suspected cases of acute brucellosis. Agglutinins

may appear as early as the fifth day of illness, but ordinarily are not found until the second week after the onset. In some instances, specific agglutinins may not appear for several weeks. One important source of difficulty in interpreting the results of agglutination tests is the fact that agglutinins may be persistently absent or may be present in low titer in persons from whom *Brucella* has been cultivated. Another source of error in interpreting the agglutination reaction is the fact that the titer may remain at a high level for months or years after recovery. Then, too, some individuals exposed to the infection may develop agglutinins without notable illness. Furthermore, the level of the agglutinin titer may fluctuate widely on repeated testing. *These considerations call for the exercise of keen judgment in interpreting the results of the agglutination test. A person suffering from some disease other than brucellosis may have a positive agglutination test merely as the result of a previous symptomatic or asymptomatic Brucella infection.*

In the past, diagnostic significance has usually been attributed to titers of 1:80 or above. The choice of such an arbitrary diagnostic titer is not justified in the light of recent studies. In those cases in which the clinical manifestations suggest brucellosis, the absence of agglutinins or their presence in titers of 1:10 to 1:40 should stimulate further bacteriologic and serologic studies.

The difficulties which attend the interpretation of agglutination tests in cases of acute brucellosis are greatly multiplied in cases of chronic brucellosis. While the great majority of patients with the acute form of the disease reveal a positive agglutination test in high titer, a high proportion of patients with chronic brucellosis give repeatedly negative agglutination reactions or positive tests in low titer. In a group of 28 cases of chronic brucellosis studied by Evans,[60] 46 per cent gave a negative agglutination reaction.

The occasional cross agglutination of *Brucella* and *Bacterium tularense* should be borne in mind. In cases of tularemia the relatively higher titer with the *B. tularense* antigen and the usually typical history leave little doubt as to the interpretation of the serologic findings. If the *Brucella* and *B. tularense* titers are the same, or nearly so, agglutinin absorption tests will distinguish between them.

While the agglutination test is undoubtedly of great value, its limitations must be recognized. Otherwise, errors will be made in two directions: first, the correct diagnosis of brucellosis may not be made because too much reliance is placed in a negative test; or second, an incorrect diagnosis of brucellosis may be made in a person who has a residual agglutinin titer from a previous invasion by Brucella, but who is suffering from some other disease when the test is made.

The *intradermal* test is used to determine cutaneous hypersensitiveness to specific *Brucella* antigen. A positive allergic skin reaction is generally accepted as evidence of past or present invasion of tissues by *Brucella*. While the great majority of patients from whose blood *Brucella* has been recovered

show a positive skin test, the test has yielded negative results in rare instances in which *Brucella* infection was proved by culture.

The chief sources of error in interpreting the significance of a positive skin test lie in the fact that the test is frequently positive in exposed individuals with no history of an illness compatible with brucellosis. Furthermore, the hypersensitiveness, once acquired after symptomatic or subclinical infection, usually persists for many years. *Therefore, it must be emphasized that a positive skin test does not mean that the symptoms from which the patient is suffering at the time of a positive skin test are necessarily due to brucellosis.* Students of this disease are only too familiar with instances in which a diagnosis of brucellosis was made only on the basis of a positive skin test and in which further developments revealed the presence of some such disease as active tuberculosis, Hodgkin's disease, leukemia, typhoid fever, malaria, or subacute streptococcic endocarditis. Gould and Huddleson [52] regard the skin test as the most sensitive diagnostic test for brucellosis; these investigators express the belief that if the skin test is negative, brucellosis may usually be ruled out.

A variety of antigens has been used for skin testing. The two agents most commonly employed are (1) a heat-killed suspension of *Brucella* in physiologic saline solution (vaccine) and (2) a suspensoid of nucleoprotein isolated from *Brucella* by chemical separation, known as Brucellergin (Huddleson). If commercially available vaccines are used for skin testing, the usual procedure is to dilute the vaccine in a proportion of one part vaccine to nine parts sterile physiologic solution of sodium chloride and to inject 0.1 c.c. of the diluted suspension intracutaneously in the ventral surface of the forearm. It is important to select properly standardized vaccines from a reliable source. Variations in the manner of preparation, potency and dosage have led to a lack of uniformity in the production and interpretation of cutaneous reactions. The Brucellergin test is also performed by injecting 0.1 c.c. into the skin of the forearm. A positive reaction by either method is characterized by the development of a circumscribed erythematous, edematous, indurated area at the site of injection. In a positive test, the area of local reaction averages about three-fourths of an inch in diameter, but may vary from one-half inch to three or more inches. The reaction usually reaches its greatest intensity in 24 to 48 hours; ordinarily it is best to observe the results of the test 48 hours after injection. The presence of mild, transient erythema, without edema and induration, is of no significance. In frankly positive cases the induration usually persists for several days. In hypersensitive persons a positive test may be accompanied by a mild, or in some instances a severe, systemic reaction. In such cases the lymphatic channels above the site of inoculation may become red, thickened and painful, and the regional axillary lymph nodes may become enlarged and tender. An exacerbation of symptoms may follow the development of a positive skin test. Focal necrosis of the Arthus type occurs at the site of inoculation in a small number of cases.

There is evidence [61, 62] that the injection of heat-killed *Brucella* for the intradermal test stimulates the production of agglutinins. Evans [44] found that the intracutaneous injection of brucellergin in 12 volunteers caused the development of opsonins in seven and agglutinins in five; in one instance the agglutinins rose from zero to a titer of 1:320. *Hence, blood specimens for serologic tests should be collected before the intradermal test is performed.*

The inadequacies of the agglutination test and the intradermal test, particularly in distinguishing between present and past *Brucella* infection, led Huddleson, Johnson and Hamann [63] to reintroduce the *opsonocytophagic reaction,* a modification of the Leishman-Veitch technic for determining the phagocytic activity of the blood in the presence of serum opsonins and homologous leukocytes. The opsonocytophagic test is employed in conjunction with the intradermal test or the agglutination test, or both, to determine the immunity status of an individual giving positive tests by either or both methods. The test is performed by mixing 0.1 c.c. of the patient's citrated blood with 0.1 c.c. of a saline suspension of living *Brucella* which have been grown for 48 hours on liver infusion agar. The suspension should contain at least six billion organisms per c.c. of physiologic saline solution (pH 7.0). The mixture is then incubated at 37° C. (98.6° F.) for 30 minutes, after which a small amount of the sedimented cells is removed with a capillary pipette. A smear is then made from a large drop of the cell suspension, dried rapidly and stained with Hasting's stain or Bordet-Gengou's carbol toluidin blue. The number of bacteria in 25 polymorphonuclear neutrophilic leukocytes is determined and classified according to the number of bacteria per polymorphonuclear leukocyte; the absence of phagocytosis indicates a negative result; 1 to 20 phagocytized bacteria indicate slight, 21 to 40 moderate, and 41 or more, marked phagocytosis.

According to Huddleson's interpretation, the opsonocytophagic power of the blood is low during the active infective phase of the disease and becomes marked after recovery. On this basis, it is considered that individuals have developed immunity to *Brucella* if 60 per cent or more of the polymorphonuclear leukocytes show marked phagocytosis. If as many as 40 per cent of the leukocytes show moderate to marked phagocytosis the patient may be infected and has not yet developed any immunity, or he may be uninfected.

While theoretical considerations lend support to the contentions of Huddleson and his associates as to the value of the opsonocytophagic test, it still lacks confirmation. The studies by Calder,[38] and Keller, Pharris and Gaub [64, 65] appear to provide some support to Huddleson's thesis. On the other hand, Evans [60] regards the opsonocytophagic test as the least reliable of the diagnostic tests in cases of chronic brucellosis; she found strongly positive (immune) reactions in four cases from which *Brucella* were cultivated, and weak or moderate reactions in recovered cases. Morales-Otero and Gonzalez [66] tested over 200 individuals (cattle handlers, milkers and laboratory workers exposed to *Brucella* infection) with a purified *Brucella* skin-test antigen, agglutination tests, complement fixation tests and opsonocytophagic

tests. They found no correlation between cutaneous allergy to *Brucella* and the opsonocytophagic reaction. Fifteen cases that were positive to the opsonocytophagic reaction gave a negative cutaneous reaction, while 18 showing a positive cutaneous reaction were completely negative to the opsonocytophagic reaction. Lee Foshay [67, 68] and the writer, working independently, have found that a significant proportion of patients yield aberrant and unexpected results in relation to their immunity status when the opsonocytophagic test is employed in conjunction with cultural methods, agglutination tests and skin tests. High phagocytic titers (immune reactions) occur in some patients with severe and uninterrupted brucellosis, proved by cultures. Certain recovered patients, asymptomatic for months or years, exhibit marked fluctuations from month to month, running the entire gamut from high to low phagocytosis, or sometimes none at all. *Until more extensive studies have been made on culturally proved cases of brucellosis the results of the opsonocytophagic test should be interpreted with caution and with reservations.*

Hematocytologic studies indicate that leukopenia occurs in the majority of patients with acute brucellosis. In chronic brucellosis, either leukopenia, moderate leukocytosis or normal leukocyte levels may be found. Calder [69] has directed particular attention to the occurrence of active lymphocytogenesis as the most striking and constant feature of the blood picture in all of the manifestations of brucellosis. The lymphocytosis is evidenced by an increase in both percentage values and in absolute numbers of lymphocytes and by an unusually high proportion of immature lymphocytes (lymphocytic shift-to-the-left). Mild anemia of the macrocytic, hyperchromic type is the rule. The erythrocyte sedimentation rate is usually not high, except when regional complications are present. Calder expresses the belief that this combination of white blood cell and red blood cell abnormalities is distinctive for brucellosis and provides an additional confirmatory diagnostic aid.

Prognosis

Fatal outcome is rare, having occurred in about 2 per cent of reported cases. During 1936, 107 deaths from brucellosis were officially recorded in the United States. The importance of the disease is not to be judged by the low mortality rate. The prolonged course and the resulting chronic ill health in a high proportion of cases make the outlook much more serious than the death rate would indicate. Death is usually the result of overwhelming acute infection, terminating fatally during the first few weeks of illness, or it follows a relapse at any stage of the disease due to regional localizations of *Brucella* in such structures as the meninges, brain, heart valves or lungs.

Treatment

The most important consideration in the control of brucellosis is *prophylaxis*. The widespread distribution of the infection among cattle renders it

difficult to control the infection at its source. Many cows have Bang's disease and eliminate the organisms in large numbers in the milk and vaginal discharges without manifesting symptoms of the disease (abortion, mastitis, sterility and lessened milk yield).

Since 1934, the United States Department of Agriculture has been engaged in a laudable campaign directed toward eradication of brucellosis in cattle. After 55 months of diligent effort, ending January 31, 1939, more than a million and a half cattle (approximately 5.5 per cent of the number tested) were found to give positive tests for brucellosis; the infected cattle were condemned and the farmers and dairymen received indemnities to compensate for the loss of the cattle. Unfortunately, no similar campaign has yet been inaugurated to control the disease in hogs and goats.

The logical method for preventing the transmission of milk-borne infection to human beings is by pasteurization. Brucellosis is only one of the formidable list of diseases transmitted to man through the use of raw milk and other unpasteurized dairy products. Murray, McNutt and Purwin,[70] Boak and Carpenter,[71] and Zwick and Wedeman[72] have demonstrated that complete pasteurization (143–145° F. (61.6–62.7° C.) for 30 minutes) will destroy *Brucella. The need for strict supervision of the pasteurization process is apparent.* For the protection of the health of those persons whose occupations bring them in direct contact with infected animal tissues we must rely upon education and the institution of precautionary measures.

For those persons who live on farms, or in small communities where pasteurization is not yet practiced, home pasteurization may be carried out by placing the milk in an aluminum vessel and heating it to 155° F. (68.3° C.), stirring constantly, then immediately setting the vessel in cold water and continuing the stirring until cool.

Prophylactic Immunization

Kolmer, Bondi and Rule[73] have recently reported the apparently successful simultaneous immunization of human beings against both brucellosis and typhoid fever by administering a vaccine composed of 1,000 million heat-killed *B. typhosus* combined with similar quantities of heat-killed *Br. abortus* and of *Br. melitensis.* The vaccine was administered subcutaneously in doses of 0.5, 1 and 1 c.c. at weekly intervals. The vaccination was well borne; the mild reactions were comparable to those following typhoid-paratyphoid vaccine. About 96 per cent of the subjects developed agglutinins for *B. typhosus* and all developed both agglutinins and immune opsonin for *Br. abortus.* The serums of about 17 per cent showed some protective antibody for *Br. abortus* before immunization as compared with 79 per cent after immunization. Similarly, some protective antibody for *Br. melitensis* was present in 14 per cent of the volunteers before vaccination; after immunization all had protective antibody. Immunization with the vaccine did not appear to produce allergic cutaneous sensitization to brucellergin. These

observations would appear to justify more extended trial of this simple method of protection, particularly for those who are exposed to either typhoid or *Brucella* infection.

Specific Therapy

While there is considerable evidence that the employment of various types of serum therapy and vaccine therapy has greatly improved the outlook for most patients suffering from acute or chronic brucellosis, it is extremely difficult to evaluate the effectiveness of any form of specific therapy in a disease characterized by natural remissions and by an extremely variable symptomatology. The reported results of vaccine therapy or serum therapy run the entire gamut from pessimism to hyperenthusiasm. More extensive controlled and systematic studies on a large number of patients, carried out over a period of many years, are necessary before definite statements can be made. It would appear, however, that sufficient data have been accumulated to justify the continued and extended use of some of the specific agents.

A. Serum Therapy

Interest in serum therapy, which had waned following the earlier appearance of several unfavorable reports, has been revived by the development of a more potent anti-*Brucella* serum by Foshay [74, 75] and his associates at the University of Cincinnati. Detoxified *Brucella* antigens are employed for the development of the antiserums in goats or horses. Several favorable experiences with the Foshay serum have been recorded by other workers.[76–80] This type of antiserum therapy should be restricted to patients with acute or subacute brucellosis, preferably to those who have had the disease less than eight months. The dosage recommended by Foshay is as follows: for adults suffering from moderately severe to severe manifestations of the disease, the average total dose is 60 c.c., given by three daily intravenous or intramuscular injections of 20 c.c. each or by two daily injections of 30 c.c. each; in unusually severe infections, 90 to 120 c.c. may be given in unit doses of 30 c.c. during a period of 48 to 72 hours; for children, a total of 20 to 30 c.c. may be given, either intramuscularly or subcutaneously, in daily doses of 10 c.c. each.

Serum therapy is not indicated in cases of chronic brucellosis of more than eight months' duration, unless sudden, severe exacerbations occur. Such abrupt relapses are usually the result of regional localizations involving the meninges, brain, spinal cord, heart valves, lungs, liver, spleen and bone marrow. In such cases, the dosage of serum would be that recommended for unusually severe infections.

B. Vaccine Therapy

It seems probable that the earlier discrepant reports of the effectiveness of vaccine therapy had their basis in a lack of standardized methods for the

preparation of the vaccines, both as regards the choice of suitable strains and the concentration of the vaccine. These difficulties appear to have been largely overcome in recent years by the development of better standards for the preparation of therapeutic vaccines.

Brucella melitensis (varieties *abortus* and *suis*) vaccine, N. N. R., has been widely employed and is available through the usual trade sources. This vaccine is a saline suspension of heat-killed or formalin-killed *Brucella abortus* and *suis* organisms in equal quantities. Vaccines prepared from the *melitensis* variety of the organism should be utilized only in the treatment of the relatively rare *Brucella melitensis* infections.

Experience has taught that no rigidly standardized scheme of dosage of vaccine is applicable to patients with brucellosis. Experience and good judgment are essential requisites in determining the proper dosage for each individual. The usual procedure with the commercially available vaccine is first to test for hypersensitiveness by injecting 0.05 c.c. of a 1 : 10 dilution of the vaccine intracutaneously. If the patient does not experience an excessive local or systemic reaction within the next 48 hours, an initial therapeutic dose of 0.25 c.c. is injected into the deep subcutaneous tissues, or preferably into the muscle. Local reactions are minimized by intramuscular injections. If no untoward reaction follows the first injection of 0.25 c.c., a second dose of 0.25 c.c. is given three days later. The dosage is then increased in increments of 0.25 c.c., at intervals of three days, until a dosage of 1 c.c. is reached. Ordinarily, two injections of 0.5 c.c. and two of 0.75 c.c. are given before the 1 c.c. dosage is attained. Five to eight injections of 1 c.c. each may then be given at three-day intervals.

If the patient is highly sensitized, it is wise to begin with intramuscular doses of 0.1 c.c., or, in rare instances of extreme sensitization, with doses of 0.1 c.c. of a 1 : 10 to 1 : 100 dilution of the vaccine, and gradually increase the dosage by 0.1 c.c. increments until a dosage of 1 c.c. is reached. If, during the course of vaccine injections an unusually severe local or systemic reaction should occur it is desirable to reduce the next dose to one-half the amount which produced the severe reaction and then cautiously and gradually increase the succeeding doses.

A series of four to six or more sharp systemic, febrile reactions, usually accompanied by a transient exacerbation of symptoms, is the goal of the treatment. Hence, only extreme local or general reactions should be avoided. Elevations of temperature to 103–105° F. (39.4–40.6° C.) are not uncommon within four to eight hours after the injection of vaccine. Such systemic responses may occur following the first injection of a small quantity of vaccine or may not occur until relatively large doses are given. In chronic brucellosis larger doses of the vaccine may be required; if no reaction is provoked after five or six 1 c.c. injections, the dosage may be gradually increased by 0.5 c.c. increments to 2 or 3 c.c.

While some patients who have obtained an apparently satisfactory response to vaccine therapy have had little or no thermal reaction, the most prompt and lasting results have occurred in those who have experienced several such reactions.

Erythema and tenderness at the site of vaccination occur commonly for a day or two following injections. In about 5 per cent of cases, a local hard tumefaction may persist for much longer periods. In a small proportion of such cases sterile abscesses or local areas of necrosis have developed.

C. Brucellin Therapy

Brucellin is a fraction of *Brucella* cells obtained by growing the organism in liver broth. The bacteria-free active agent is recovered from the liver broth filtrate. This preparation was devised by I. F. Huddleson [81, 82, 83] and may be procured at the Central Brucella Station, Michigan State College, East Lansing, Michigan.

The dosage of Brucellin must also be adjusted to suit the requirements of individual patients. After the extent of sensitiveness has been determined by the intradermal injection of 0.1 c.c. of Brucellin, the usual procedure in non-hypersensitive patients is to give repeated injections of 1 c.c. at intervals of three days until the morning and evening temperatures between the intervals of injection tend to become subnormal. Here again, one object of this form of therapy is the production of a series of four or more febrile, systemic reactions. If the duration of illness is less than 10 weeks, the likelihood of recovery following four 1 c.c. injections is greater than if the duration is longer than 10 weeks. Patients with long-continued chronic brucellosis require a larger number of injections and may require gradually increasing amounts up to 5 c.c. before satisfactory reactions are produced. In highly sensitized persons, it is advisable to start with intramuscular doses of 0.1 c.c. If there is no severe systemic reaction following this injection, each succeeding dose may ordinarily be doubled, until the larger dosage is attained.

A partially oxidized detoxified vaccine, devised by Foshay and O'Neil,[84] has been used with apparent success.[38] Much smaller doses are given subcutaneously at more frequent intervals. The few reports of results indicate the recovery rate equals that of other vaccines or Brucellin. Local or constitutional reactions do not occur with the oxidized vaccine. It has been recommended chiefly for the treatment of chronic brucellosis.

While it is difficult to evaluate the results of vaccine or Brucellin therapy, the experiences of many investigators indicate that about 60 per cent of patients with brucellosis obtain apparently complete recovery after a satisfactory course of either agent. An additional 25 per cent appear to obtain some benefit, while the remaining 15 per cent are not improved.

The contraindications to vaccine or Brucellin therapy are heart disease, renal disease, arteriosclerosis, meningeal or cerebral localizations of *Brucella* or the acute fulminating (malignant) form of the disease.

Non-Specific Protein Therapy

Injections of foreign protein substances, such as sterile skimmed milk, typhoid vaccine or typhoid-paratyphoid vaccine have been utilized [85, 86, 87] for the production of non-specific shock reactions in the treatment of brucellosis. Erwin and Hunt [88, 89] reported good results in 20 patients with acute and subacute brucellosis following the intravenous injection of killed typhoid paratyphoid organisms. The usual initial dose was 30 to 50 million killed organisms, with two to six additional injections, increasing the dosage by increments of 25 million organisms.

Chemotherapy

Neoarsphenamine, mercurochrome, acriflavine, metaphen, thionin, methylene blue, methyl violet, gentian violet and other chemical substances have been used in the treatment of brucellosis. In most instances the reports of the apparently successful use of these substances were based upon observations limited to small numbers of patients. The very length of the list argues against the specificity of any of them.

Sulfanilamide and related compounds have been heralded [90] as effective agents in the treatment of brucellosis since 1936. After the first wave of enthusiasm, usually based on short observations on relatively few patients, other reports of less favorable or entirely negative results have appeared. Blumgart and Gilligan [91] analyzed the results reported in the 31 papers which appeared between 1936 and 1939. Twenty-four of the reports were concerned with only one or two patients. Of the 74 cases treated with sulfanilamide or allied compounds, there were 68 apparent recoveries and six failures; 14 of the 68 patients (20 per cent) exhibited relapse after apparent recovery. The daily dosage of sulfanilamide employed in most cases was 4 to 6 gm. (60 to 90 grains) during the period of fever, with gradually diminishing dosages for three or four days after the fever abated. The administration of the drug was rarely continued for more than 12 days. Bynum [92] reported six cases of brucellosis unsuccessfully treated with large doses of sulfanilamide. Long and Bliss [93] report recurrence of infection in four of five patients whose immediate response to sulfanilamide therapy was apparently quite satisfactory; in two instances *Brucella* was recovered from the blood after sulfanilamide therapy was discontinued. The writer has had similarly disappointing experiences in several cases treated with large doses of sulfanilamide, sulfapyridine or sulfathiazole, controlled by quantitative blood levels; in several instances apparent remission occurred only to be followed by relapse. *Until more extensive and extended studies are made on culturally proved cases, the value of sulfonamide therapy in cases of brucellosis must be regarded as undetermined.* In this connection it might be well to recall the fact that a temporary remission is not synonymous with cure.

Artificial Fever Therapy

The observation that recovery from brucellosis often followed the induction of fever by chemical or biological agents led Prickman and Popp [94] to investigate the possible usefulness of artificial fever induced by physical means in the management of brucellosis. Each of three patients was given three artificial fever treatments, each of five hours' duration, at a rectal temperature of 105–106° F. (40.6–41.1° C.); all were benefited by the treatment. Zeiter [95] described a similarly favorable experience. More recently, Prickman, Bennett and Krusen [96] analyzed the results of treatment with physically induced hyperpyrexia in 21 cases of brucellosis; apparent cure resulted in 80.9 per cent of the patients. The duration of the disease prior to artificial fever therapy varied from 10 days to two and one-half years. We [97] have had similar favorable results in refractory patients who have not responded to vaccine therapy; the usual course employed by us has consisted of six fever sessions, each of three hours' duration, at a rectal temperature level of 105° F. (40.6° C.), given during a period of two weeks; the patients were hospitalized during the course of artificial fever treatments. Artificial fever therapy should be carried out only in properly equipped institutions by thoroughly qualified physicians and nurse-technicians.

Summary and Conclusions

1. The author's prediction of a decade ago, greeted with some skepticism at that time, that brucellosis would become recognized as a public health problem of major proportions has been fulfilled. Of the 248 cases of brucellosis studied by the author, all but 52 occurred prior to the passage of a universal pasteurization ordinance in 1931. In all but one of the 52 cases occurring during the past 10 years the patient had consumed raw milk elsewhere prior to the onset of illness; the exceptional patient was a dairy employe who drank milk before it was pasteurized.

2. The symptomatology of the acute and the chronic forms of brucellosis varies greatly. The diagnostic criteria for acute brucellosis are usually not applicable to the chronic form of the disease. There is little doubt that the chronic ambulatory form of brucellosis is widely prevalent, is often confused with other diseases, and frequently is not recognized. Many "neurasthenics" and patients with so-called "fever of unknown etiology" have been found to be victims of chronic brucellosis. Less than 10 per cent of patients with chronic brucellosis have experienced a previous acute febrile illness, compatible with a diagnosis of acute brucellosis.

3. The only diagnostic procedure by which the diagnosis of brucellosis may be established with certainty is by the cultivation and identification of the organism. The agglutination test and skin test are of considerable value in the diagnosis of acute brucellosis, but these procedures are notoriously inadequate as diagnostic aids in cases of chronic brucellosis. A positive agglutination test, particularly of low titer, and a positive skin test do not indi-

cate that the person is suffering from brucellosis at the time the tests are made. Both the agglutination test and the skin test will yield entirely negative results in an appreciable number of persons from whose blood *Brucella* may be recovered.

4. In our hands, the opsonocytophagic test has yielded a high proportion of inconsistent results. We have found this test to be of little value as a diagnostic procedure or as a guide to therapeutic response.

5. Since it is now well established that brucellosis is caused most frequently in this region by the ingestion of raw milk containing *Brucella*, the most important consideration in the control of the disease is adequate, controlled pasteurization of all milk and dairy products.

6. *Brucella* vaccine therapy has produced favorable results in from 60 to 85 per cent of patients with either acute or chronic brucellosis. Sulfanilamide and other sulfonamide drugs are apparently of little benefit. Artificial fever therapy has yielded favorable results, particularly in those refractory patients who did not respond to vaccine therapy.

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THE SULFONAMIDE THERAPY OF STAPHYLOCOCCAL SEPTICEMIA *

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Introduction

The history of medicine probably contains no parallel example of the generalized acceptance and popularity of a treatment as that of the sulfonamide derivatives. While there can be little question of the efficacy of these drugs in certain infections, it is becoming increasingly apparent from the slowly accumulating reports of more conservative observers, that the exaggerated faith in their panaceal capacities does not appear to be justified, as, indeed, recent critical reviews illustrate.[1-3] Among the different communications devoted to sulfonamide therapy, a number of scattered reports have dealt with the successful treatment of staphylococcal septicemia. Consisting to a great extent of individual case histories, scanty in detail and relevant information, the reports are difficult to appraise in regard to the actual value of the sulfonamides in this form of infection. This becomes even more difficult when it is realized that while successes are reported, failures usually are not, thus presenting the reader with a one-sided point-of-view.

While studying the effect of an experimental, antibacterial serum[4] on staphylococcal septicemia, there have been referred from time to time to the present writers patients in whom the sulfonamide drugs were frank failures in checking the course of infection. With the number of such patients mounting steadily, a feeling of doubt was created regarding the degree of effectiveness of any of the sulfonamides thus far introduced to control severe staphylococcal infection. It was decided, therefore, to analyze the data on hand in order to ascertain the exact conditions and results of the drug therapy. It must be said in fairness that the criticism applied above to the one-sided reporting of successful treatment is equally tenable in this instance, since the cases to be described herewith represent unsuccessful treatment, only. In justification of this position, however, it must be remembered that *genuine* staphylococcal septicemia is not common, so that the relatively large number of patients, as will be reported below, may be a better indication of the probable outcome awaiting the treatment of such infection with these drugs than appears on the surface.

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Review of the Literature

Before considering the statistical evidence in the hands of the writers, it may be of value to review briefly the experience of preceding workers. That presentation of their results may be simplified, the available data derived from 27 different references have been arranged in tabular form (table 1).

Table I

Collected Statistics on Effect of Sulfonamides in Staphylococcal Septicemia

Investigators	Drug Studied	Number of Patients	
		Treated	Recovered
Foerster [5]	Prontosil	1	1
Mitchell [6]	Uleron	3	3
Colebrook and Kenny [7]	Sulfanilamide	3	2
Mendell [8]	"	3	0
Thornhill et al.[9]	"	2	2
Blake and Haviland [10]	Sulfapyridine	5	0
Fenton and Hodgkiss [11]	"	1	1
Galewski and Stannus [12]	"	1	1
Goldberg and Sachs [13]	"	2	2
Hartmann et al.[14]	"	2	2
Long [15]	"	5	3? (rapid sterilization)
Martin and Bryan [16]	"	5	4
O'Brien and McCarthy [17]	"	1	1
Spink, Hansen, and Paine [18]	"	10	6
Wade [19]	"	1	1
Carroll et al.[20]	Sulfamethylthiazole	3	3
Hartmann [21]	"	8	3
Herrell and Brown [22]	"	1	1
Weisman and Russell [23]	"	2	2
Carey [24]	Sulfathiazole	6	3
Fitch [25]	"	1	1
Keliher and Carlan [26]	"	1	1
Rammelkamp and Keefer [27]	"	7	3
Scott [28]	"	1	1
Spink, Hansen, and Paine [18]	"	19	18
Stirling [29]	"	1	1
Abramson and Flacks [30]	Different compounds	6	2
Herrell and Brown [31]	" "	27	15
Totals		128	83

If the figures are accepted at their face value, it is seen that a total of 128 cases are recorded as having been treated with one or another of the sulfonamide compounds, and of these 83 recovered, presumably because of the drug therapy, thus demonstrating an effective rate of these compounds of close to 65 per cent. This is obviously an impressive ratio, approximately reversing the usual figures for fatality and survival in staphylococcal septicemia. However desirable it may be, it is impossible to attempt further analysis, since with few notable exceptions,[10, 18, 21, 27, 31] the publications summarized lack sufficient information for the purpose. It is nevertheless interesting that in a number of instances, diagnosis of septicemia was based on a single, positive

blood culture, and in one case, only one of several blood cultures yielded growth, and then a single colony of *Staphylococcus*. The optimum blood concentration of the drug attained varies with the different reports from 3 mg. (27) to 6 mg.[18] to 20 mg.[31] per 100 c.c. of blood. While the number of cases is too few for statistical evaluation, the impression gathered is that sulfathiazole shows the maximum effect, this impression strengthened by the high degree of success with this drug reported by Spink, Hansen, and Paine.[18] The majority of the publications represents small numbers of patients, even though in the aggregate, a considerable figure is reached. Unfortunately, however, it is more than likely that for the most part the reports were made primarily to point out the therapeutic effectiveness of the drugs. Failures experienced by other observers, on the other hand, are not to be found in print, if it is fair to judge from the number of personal, unsolicited communications received by the writers from various physicians in this country. Consequently, while the degree of efficiency as represented in the literature is undoubtedly high and gratifying, it must be remembered that the picture is incomplete.

Observations and Results

In preparing the data of the present communication for analysis, it was found convenient to tabulate the patients under the particular drug employed. Diagnosis of septicemia was based on several daily blood cultures yielding staphylococci, and in most cases the additional technic was incorporated of plating measured amounts of blood to determine the number of colonies per c.c. of blood. The significance of the culture was subsequently established by the fermentation of mannite [32] and by the extraction and precipitation of the specific carbohydrate (Type A) elaborated by the bacterial cell.[33] The sulfonamide drugs were given as early as possible and the dosages given, while variable, were well within the usual limits. Chemotherapy was then continued to a point where it was decided by the physician in charge that the chemotherapy was a failure, when one of the present writers was called upon for consultation. In certain patients some other form of treatment was substituted for the drug, but in such instances, the subsequent method of treatment has been tabulated only when the patient survived, or it was possible to continue the substituted treatment for a reasonable length of time to establish its effect (i.e., for at least 48 to 60 hours). It did not seem fair to include any treatment given for less than the designated period, because it was obvious that in such cases the condition was already hopeless before therapy was instituted. In addition to the drug therapy, each patient was given whatever surgical care and supportive treatment was indicated during the course of the disease.

In table 2, will be found the data bearing on the treatment of staphylococcal septicemia with sulfanilamide. It will be seen that 19 patients with septicemia arising from a variety of localized conditions were given the drug

TABLE II

Effect of Sulfanilamide on Staphylococcal Septicemia

Patient	Age	Sex	Diagnosis	Drug Treatment			Subsequent Specific Treatment	Ultimate Outcome	Comments
				Day Started	Duration (Days)	Effect			
M. C. 1	37 yrs.	F	Furunculosis Pneumonia Septicemia	8th	21	none	Phage	Died	Phage and drug treatment concurrent
C. W. 4	18 mos.	F	Primary focus ? Septicemia	3rd	15	none		Died	
V. V. 5	7 mos.	F	Septicemia	2nd	10	none		Died	
M. D. 8	35 yrs.	F	Furunculosis Renal abscesses Septicemia	1st	6	none	Antitoxin then Antibacterial serum	Recovered	Drug started first day of septicemia not furunculosis
D. K. 12	4 yrs.	F	Tonsillitis Osteo. l. tibia Septicemia	2nd	6	none	Antibacterial serum	Recovered	
C. S. 13	25 yrs.	M	Cellulitis-face Pneumonia Septicemia	2nd	10	none	Antibacterial serum	Recovered	
A. M. 16	63 yrs.	M	Infected nose Pneumonia Septicemia	3rd	8	none	Antitoxin 7 days	Died	
W. N. 25	21 yrs.	M	Infected finger Extension along arm Pneumonia Septicemia	3rd	4	none		Died	
V. C. 26	24 yrs.	F	Self abortion Osteo. l. hip Pneumonia Septicemia	3rd	4	none	Antibacterial serum	Recovered	
M. A. 27	10 yrs.	M	"Scarlet fever" Pneumonia Pleurisy Septicemia	3rd	8	none		Died	
D. R. 31	26 yrs.	F	Sore throat Cervical adenopathy Pneumonia Septicemia	9th	5	none		Died	Drug started 1st day of septicemia; discontinued because of toxic reactions
P. V. 35	57 yrs.	M	Infected thigh Cellulitis Thrombophlebitis Septicemia	7th	5	none	Antibacterial serum	Died	
H. J. 48	44 yrs.	M	Cellulitis l. foot and leg Pneumonia Pleurisy Septicemia	1st	5	none	Antibacterial serum	Died	
R. W. 63	5 yrs.	M	Osteo. l. knee Septicemia	2nd	6	none	Antibacterial serum	Recovered	
S. B. 75	6 yrs.	F	Cellulitis-face Sinus thrombosis Basilar meningitis Septicemia	3rd	2	none		Died	
F. B. 80	9 yrs.	M	Osteo. foot Septicemia Endocarditis	2nd	6	none		Died	
M.-C 5	14 yrs.	F	Osteo. rib Pleurisy Septicemia?	?	10	?		Recovered	Septicemia questionable (See text)
M.-C 12	47 yrs.	F	Diabetes Furunculosis Septicemia	1st	10	none		Died	
J. N. 95	24 yrs.	F	Post-abortal infection Septicemia	1st	7	none	Antibacterial serum	Died	Endocarditis obvious after serum was started

from the first to the ninth day of illness, and this therapy was continued for variable periods up to 21 days. In each case but one (M.–C 5) sulfanilamide had failed to check infection. This was particularly striking in certain patients (M.D. 8, D.K. 12, D.R. 31, H.J. 48, M.–C 12), since the septicemia in these cases developed as a secondary complication while the drug was being administered to restrain what was at the time a purely localized infection. With sulfanilamide exerting no apparent benefit, recourse was had to other therapeutic agents as specified: bacteriophage in one, antitoxin in two, antibacterial serum in eight. The only success obtained was with the latter in that of the eight, five recovered and three died. In the remaining nine cases, reported as having no subsequent specific treatment, some actually had no other treatment or the treatment was not continued sufficiently long to consider the attempt a fair trial. In one patient (M.–C 5) recovery occurred following 10 days of treatment with sulfanilamide. This case, however, was considered as a transient bacteremia, because of 10 consecutive daily cultures, the first, fourth, and eighth were positive with never more than three colonies per c.c. of blood, and the remaining cultures yielded no growth. The indications are, therefore, that in this group of 19 patients treated with sulfanilamide, the drug certainly did not offer any protection against the infection in 18 cases, and possibly not even in the nineteenth.

The data relating to the use of sulfapyridine will be found in table 3. Analysis reveals that 12 individuals were treated with this derivative, the treatment being started on the second to the seventh day of illness and lasting from four to 28 days. In this series also are to be found examples of septicemia developing during drug treatment (M.S. 28, R.S. 45). Of the 12 patients, one was later given antitoxin and died, while seven received antibacterial serum with four survivals and three deaths. A careful review of the individual clinical records leaves no alternative but that sulfapyridine accomplished little, if anything, in this group of patients.

Possibly due to the early withdrawal of sulfamethylthiazole from circulation, the present records include only two examples of treatment with this drug (table 4). Both patients received the drug as the only specific measure. One (M.B. 1) starting with a localized infection developed septicemia during administration of the drug, while the other was an instance of rapid, fulminating infection. Both alike were unaffected by the treatment.

As will be seen in table 5, 20 patients were treated with sulfathiazole. The time of starting the drug varied from the first to the seventh day of illness, and the duration of treatment varied from four to 29 days. Two patients subsequently received antitoxin and both died. Antibacterial serum was substituted for the drug in nine patients, and of these seven recovered. The remaining nine, representing drug treatment alone or supplemented with some other specific agent at too late a stage to help, all died.

Table 6 represents patients treated with a combination of sulfonamide compounds. Thus, three received sulfanilamide and sulfapyridine, three

TABLE III

Effect of Sulfapyridine on Staphylococcal Septicemia

Patient	Age	Sex	Diagnosis	Drug Treatment			Subsequent Specific Treatment	Ultimate Outcome	Comments
				Day Started	Duration (Days)	Effect			
B. O. 24	23 yrs.	F	Pneumonia Septicemia Meningitis Endocarditis	3rd	7	none		Died	
M. S. 28	6 yrs.	F	Pneumonia Pleurisy Septicemia	3rd	5	none	Antibacterial serum	Recovered	
A. R. 29	35 yrs.	M	Pneumonia Septicemia	2nd	10	none		Died	
S. S. 30	49 yrs.	F	Infected needle prick Pneumonia Septicemia	2nd	22	none	Antibacterial serum	Died	
D. P. 42	11 yrs.	M	Osteo. l. shoulder Pneumonia Septicemia	4th	6	none	Antibacterial serum	Recovered	
C. H. 44	28 yrs.	M	Infected pimple Septicemia	2nd	14	none		Died	
R. S. 45	12 yrs.	M	Osteo. Septicemia	3rd	5	none	Antibacterial serum	Recovered	
L. B. 49	22 yrs.	F	Carbuncle l. shoulder Pneumonia Septicemia	2nd	6	none	Antibacterial serum	Died	
D. S. 51	13 yrs.	F	Pneumonia Septicemia Endocarditis	7th	10	none	Antibacterial serum	Died	Serum administered after endocarditis
M. M. 66	12 yrs.	F	Osteo. Septicemia	3rd	6	none	Antibacterial serum	Recovered	
M. S. 78	13 yrs.	M	Osteo. r. tibia Septicemia	6th	28	none	Antitoxin	Died	
M.-C 73	47 yrs.	F	Abscess, site of thoracentesis Septicemia	2nd	4	none		Died	

TABLE IV

Effect of Sulfamethylthiazole on Staphylococcal Septicemia

Patient	Age	Sex	Diagnosis	Drug Treatment			Subsequent Specific Treatment	Ultimate Outcome	Comments
				Day Started	Duration (Days)	Effect			
M. B. 1	37 yrs.	M	G. U. infection from catheter Septicemia	2nd	16	none	none	Died	
M. B. 2	40 yrs.	F	Diabetes Furunculosis Septicemia	3rd	12	none	none	Died	

TABLE V

Effect of Sulfathiazole on Staphylococcal Septicemia

Patient	Age	Sex	Diagnosis	Drug Treatment			Subsequent Specific Treatment	Ultimate Outcome	Comments
				Day Started	Duration (Days)	Effect			
B. B. 55	32 yrs.	F	Pneumonia Septicemia	7th	15	none		Died	
L. C. 58	11 yrs.	F	Osteo. l. tibia and r. ulna Septicemia Endocarditis	4th	5	none	Antibacterial serum	Died	Serum given after endocarditis was obvious
G. O. 64			Osteo. Septicemia	5th	6	none	Antibacterial serum	Recovered	
S. T. 69	60 yrs.	M	Diabetes Carbuncle neck Pneumonia Septicemia	6th	Intermittent over 29 days	none		Died	
W. H. 72	20 mos.	M	Osteo. Septicemia	2nd	24	none	Antibacterial serum	Recovered	
T. N. 73	21 mos.	M	Infected foot Septicemia	4th	9	none	Antibacterial serum	Recovered	
M. V. 76	23 yrs.	F	Infected toe Septicemia Endocarditis	6th	6	none	Antibacterial serum	Died	Serum given after endocarditis was obvious
P. B. 77	3 yrs.	M	Osteo. Septicemia	3rd	8	none	Antibacterial serum	Recovered	
F. B. 84	37 yrs.	F	Perinephritic abscess Pneumonia Septicemia	?	12	none	Antibacterial serum	Recovered	
L. S. 87	38 yrs.	M	Gluteal abscess Septicemia	2nd	8	none		Died	
M. O. 88	40 yrs.	M	Infected finger Pneumonia Pleurisy Septicemia	3rd	10	none		Died	
W.-MC 1	4 yrs.	M	Osteo. Septicemia	4th	20	none	Antitoxin	Died	
W.-BC 2	16 mos.	M	Osteo. Septicemia	4th	12	none	Antitoxin	Died	
P. E.	20 mos.	M	Primary focus? Septicemia Pericarditis	3rd	16	none		Died	
D. F.	6 yrs.	F	Osteo. Septicemia	?	24	none		Died	
D. O.	30 yrs.	M	Cellulitis Septicemia Multiple metastatic abscesses	?	20	none		Died	
J. S. 89	7 mos.	F	Osteo. Convulsions Septicemia Metastatic abscess Agranulocytosis	6th	4	none		Died	Rapid fulminating infection
J. H. 91	6 mos.	F	Pneumonia following inhalation of foreign body Septicemia	5th	5	none		Died	Rapid fulminating infection
M. M. 94	?	F	Post-operative pneumonia Septicemia	1st	6	none	Antibacterial serum	Recovered	
E. E. 96	32 yrs.	F	Primary pneumonia Septicemia	2nd	11	none	Antibacterial serum	Recovered	

TABLE VI

Effect of Combined Sulfonamide Drugs on Staphylococcal Septicemia

A. Sulfanilamide and Sulfapyridine

Patient	Age	Sex	Diagnosis	Drug Treatment			Subsequent Specific Treatment	Ultimate Outcome	Comments
				Day Started	Duration (Days)	Effect			
J. T. 39	9 yrs.	F	Osteo. r. foot, r. scapula, l. ulna, l. fibula Septicemia	3rd	Sulfanilamide-4 Sulfapyridine-4	none	Antitoxin 4 days, then antibacterial serum	Recovered	
F. B. 43	15 yrs.	M	Osteo. Septicemia	6th	Sulfanilamide-12 Sulfapyridine	none	Phage, antitoxin, then antibacterial serum	Recovered	Sulfapyridine was given intermittently over a period of 8 weeks
M. M.	15 yrs.	M	Osteo. skull Septicemia	4th	Sulfanilamide-3 Sulfapyridine-5	none	Antibacterial serum	Recovered	

B. Sulfanilamide and Sulfathiazole

M. B. 57	11 yrs.	F	Osteo. r. hip Septicemia Pericarditis	2nd	Sulfanilamide-2 Sulfathiazole-15	none	Antibacterial serum	Died	Serum used after pericarditis was obvious
C. K. 70	3 wks.	F	Gingival abscess Osteo. r. tibia Septicemia	4th	Sulfanilamide-3 Sulfathiazole-8	none		Died	
A. T. 85	15 yrs.	M	Osteo. l. tibia Septicemia	2nd	Sulfanilamide-2 Sulfathiazole-4	none	Antibacterial serum	Recovered	

C. Sulfapyridine and Sulfathiazole

J. P. 71	8 yrs.	M	Abscess r. shoulder Septicemia	3rd	Sulfapyridine-2 Sulfathiazole-2	none		Died	

D. Sulfamethylthiazole and Sulfathiazole

D. K. 56	5 yrs.	F	Paronychia r. thumb Septicemia Pericarditis Osteo. r. femur	5th	8	none	Phage, then antibacterial serum	Died	Serum used after pericarditis was obvious
J. H.	16 yrs.	F	Osteo. l. hip Septicemia	?	12	none		Died	
J. C.	37 yrs.	F	Nephritic abscess Septicemia	5th	6	none		Died	

sulfanilamide and sulfathiazole, one sulfapyridine and sulfathiazole, and three, sulfamethylthiazole and sulfathiazole. The evidence is similar to that of the preceding tables. After unsuccessful trial with the combined drugs, three of the 10 patients were subsequently treated with antibacterial serum and two recovered; three were given combinations of phage, antitoxin, and

antibacterial serum and one recovered; the remaining four, with no other treatment, all died.

Thus, then, if all the data are summarized (table 7) it is seen that 62 patients were treated with different sulfonamide derivatives. Except for the doubtful case referred to above (M.–C 5), there appears to be little choice in the different derivatives used and little evidence for accepting this form of

TABLE VII

Summary of Sulfonamide Treatment of Staphylococcal Septicemia

Sulfa-Drug Used	No. of Patients	Effect of Drug	Subsequent Specific Treatment	Ultimate Outcome
Sulfanilamide	18	none	Phage 1	Died
			Antitoxin 1	Died
			Antibacterial serum . . . 8	5 Recovered, 3 died
			*No other treatment . . . 8	7 Died, 1 recovered?
Sulfapyridine	12	none	Antitoxin 1	Died
			Antibacterial serum . . . 7	4 Recovered, 3 died
			No other treatment 4	4 Died
Sulfamethyl-thiazole	2	none	No other treatment 2	2 Died
Sulfathiazole	20	none	Antitoxin 2	2 Died
			Antibacterial serum . . . 9	7 Recovered, 2 died
			No other treatment 9	9 Died
Combined drugs	10	none	Antibacterial serum . . . 3	2 Recovered, 1 died
			Antitoxin followed by antibacterial serum . . 1	Died
			Phage followed by antibacterial serum . . 1	Died
			Phage followed by antitoxin, then by antibacterial serum . . 1	Recovered
			No other treatment 4	4 Died
Grand totals	62	none	Phage 1	Died
			Antitoxin 4	4 Died
			Antibacterial serum . . . 27	18 Recovered, 9 died
			Combined biological agents plus antibacterial serum 3	1 Recovered, 2 died
			No other treatment 27	1 Recovered?, 26 died

* This implies that other specific treatment was not attempted, or was of too short duration to be significant. All patients received both whatever surgical care was indicated and the usual supportive measures.

chemotherapy as a strikingly specific treatment for staphylococcal septicemia. For example, of the 62 patients, 42 eventually died, the remaining 20 surviving, according to the writers' interpretation, because of other therapy. If the objection be made, however, that the sulfonamides contributed to the recovery of the surviving patients, thereby discounting completely the later treatment, the mortality rate on this basis still attains a figure of over 67 per cent. Such a result, it must be admitted, at best only matches the " average "

rate, and therefore, shows no improvement over the usual non-specific measures employed in the past.

There is no particular point to be gained at the present time by discussing the effect of the subsequent, specific measures adopted. This is part of an-

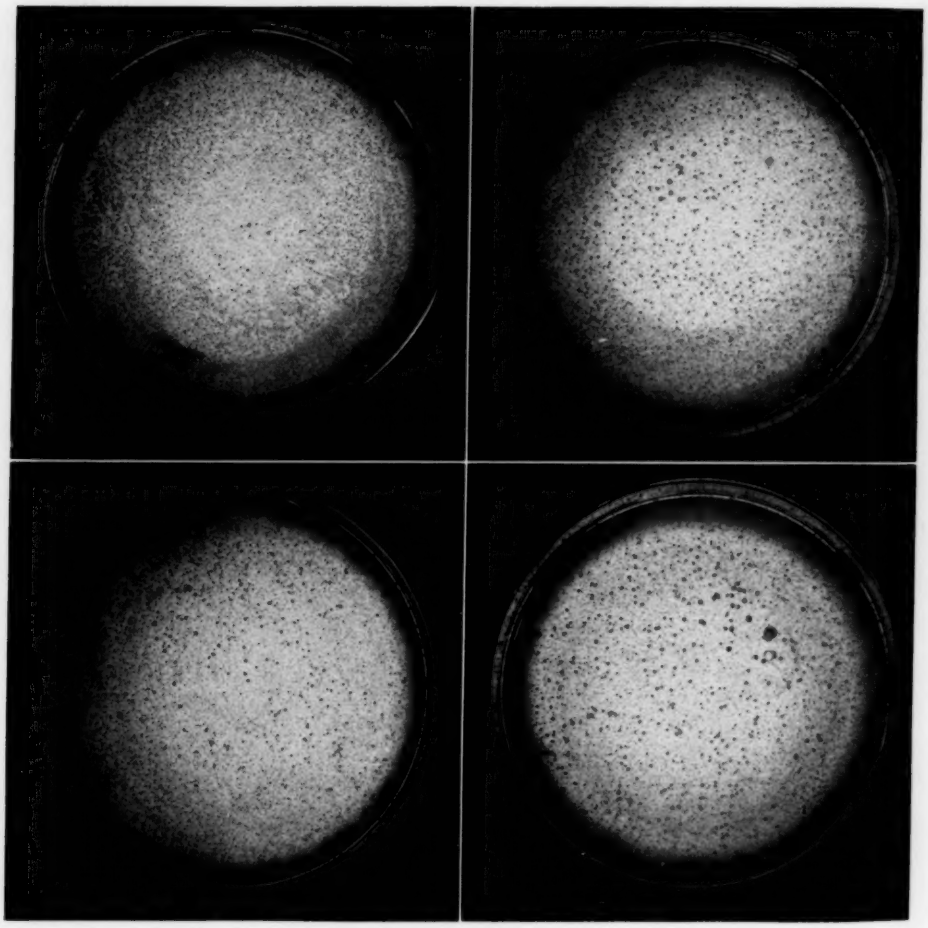

FIG. 1a. Effect of sodium sulfathiazole (30 per cent) on culture of *Staph. aureus*. 1/20,000 c.c. of culture plated before and after mixing. Upper left, before. Upper right, 2 min. after. Lower left, 15 min. after. Lower right, 60 min. after.

other investigation to be reported later. For the time being, it may suffice to say that they have been included to keep the records complete, and to demonstrate that, in the patients surviving, some treatment other than the sulfonamides was more probably responsible for recovery.

In this connection, it is of interest to describe an experiment repeated on several occasions to determine the in vitro effect of the sulfonamides on *Staphylococcus*. For this purpose the thiazole compound was particularly

studied, since by reputation, at least, it appears to be the most effective in such infections. Because of the high solubility of its sodium salts, it was used in this form. Saturated solutions (approximately 60 per cent) were used entirely, and on subsequent mixing with equal volumes of broth cul-

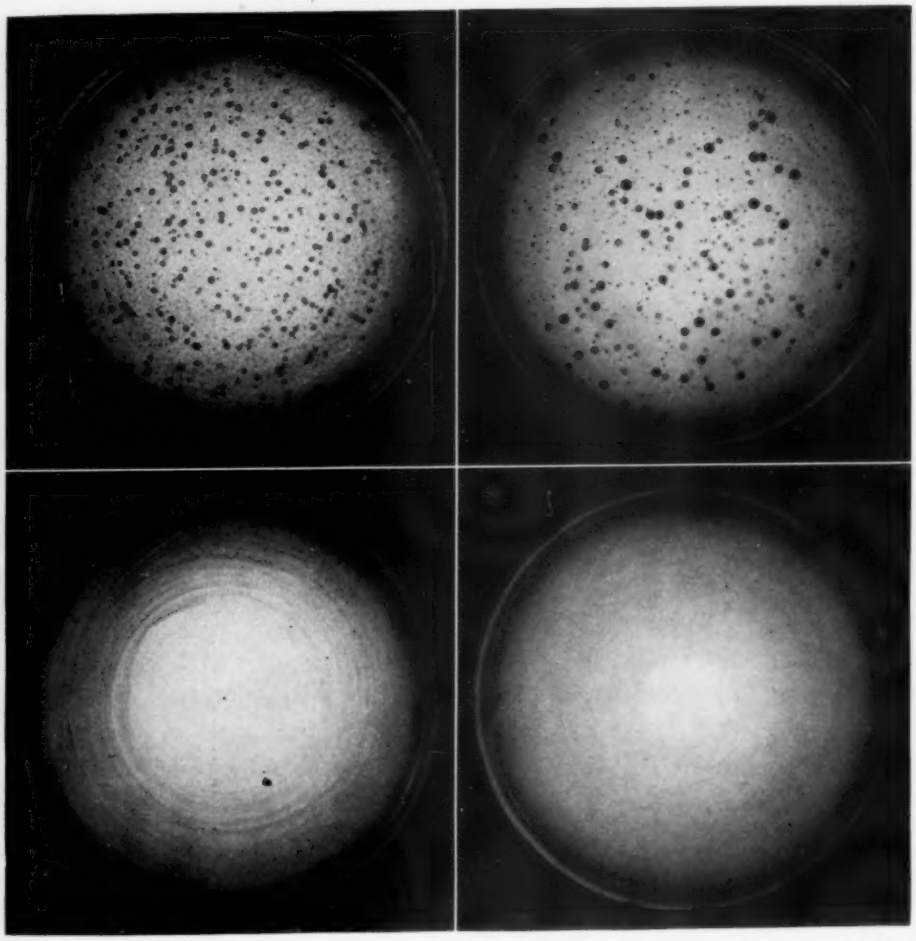

FIG. 1b. Effect of sodium sulfathiazole (30 per cent) on culture of *B. coli*. 1/20,000 c.c. of culture plated before and after mixing. Upper left, before. Upper right, 2 min. after. Lower left, 15 min. after. Lower right, 60 min. after.

ture, the concentration was accordingly reduced to 30 per cent, and the alkalinity measured from pH 10.5 to pH 11.0.

Upon mixing equal volumes of solution and culture, there was an immediate, curious effect, later recognized as an optical illusion, but originally interpreted as a solubility effect (i.e., that staphylococci are soluble in 30 per cent sodium sulfathiazole). Subsequent study revealed that actually the organisms are not dissolved, but that possibly the drug causes a change in

the refractive index of the bacteria, or the menstruum, thus giving the false appearance of a solution, an opinion, however, still remaining to be proved.

Young broth cultures (8 to 12 hours), then, were mixed in equal volumes with the sodium salt as indicated, and at specified intervals cultures were plated in meat infusion agar to determine the effect of the drug on viability of the *Staphylococcus*. Thus, cultures were made with 1/20,000 c.c. before adding the drug and at two, 15, and 60 minutes following mixing. In order to illustrate the results observed, photographs were made after 24 hour incubation of the cultures, and these are submitted in the accompanying plate. Merely a glance suffices to demonstrate that no appreciable effect was noticeable under the conditions stated. In other words, at a concentration, approximating five thousand times that in the blood of treated patients (6 mg. per 100 c.c.) and for exposures up to one hour, sodium sulfathiazole apparently altered very little, if any, the original number of staphylococci. When the exposure was continued for 20 hours, there was a decrease of about 80 per cent to 90 per cent in cultivable organisms, but this was probably due to the high alkalinity effecting dissolution of the bacterial cells. Comparable results were obtained with three different strains, each isolated from blood cultures during septicemia, and from patients not treated with sulfonamide derivatives.

For purposes of control, similar experiments were conducted with two different strains of recently isolated *B. coli*. Within two minutes, there was a remarkable diminution in the number of colon organisms, and in 15 minutes, sterilization was complete. Parenthetically, it is interesting to add that this bacterium did not give the "solubility" phenomenon noted above. The contrast in the behavior of the drug on the two species, and the implications arising therefrom are too obvious to require comment.

Discussion

Reconciliation of divergent observations is usually difficult, and more often than not, both unsatisfactory and inconclusive. This should not justify, however, either ignoring completely or dismissing casually the presence of such a situation. Admitting at the outset, that those patients benefited by sulfonamide therapy were not referred to the present writers, but only those in whom the treatment was ineffectual, it is nevertheless clear that the results reported here cast some doubt, at least, on the high percentage of effectiveness reported by other workers. Perhaps of foremost importance in this discussion is the evidence on which the diagnosis of septicemia is based. As far as blood cultures per se go, growth of staphylococci may imply either transient passage of bacteria through the circulation (i.e., bacteremia), or their prolonged presence with frequently increase in numbers (i.e., septicemia). Consequently, repeated blood cultures, with preferably an estimation of the number of colonies per c.c., become necessary, if the two phases are to be distinguished properly. This precaution, if taken

at all, was not stated by most of the preceding workers. In any case, assuming that the evidence for septicemia is unimpeachable, it must be remembered that 15 to 35 per cent of such patients recover in the absence of any but surgical and supportive treatment. Consequently, a single case or two does not carry sufficient weight for statistical purposes; and of the 27 references cited, only six [18, 21, 24, 27, 30, 31] report more than five patients. In the absence of detailed information, therefore, both clinical and bacteriological, the reader, while accepting recovery as genuine, is unable to evaluate its significance.

It seems to the writers, however, that the crux of the matter resides in one all-important consideration. Experimental observations amply demonstrate that sulfonamide derivatives possess the capacity to suppress the growth of staphylococci, not only in vitro but in vivo as well. This suppression expresses itself, however, not as a bactericidal or bacteriostatic effect, but as a temporary retardation of growth. In time, growth which has been proceeding at a delayed rate, may then occur in the usual logarithmic manner. Consequently, it is not unlikely that in occasional patients (i.e., when the virulence of the infecting organism is not too highly exalted, when septicemia is in an early stage, when the number of staphylococci per c.c. is low, when the localized lesions are surgically accessible, when the general resistance of the patient is of good quality, etc.) the effect of drugs by restraining even for a period the otherwise rapid multiplication and invasion of the organism may actually give the tissues an opportunity to marshall their own defenses. In such instances the drugs may be helpful, but not curative, since in the ultimate analysis the patient must mobilize his own protective responses if the staphylococci are to be killed and eliminated, or if the infection is to terminate with recovery. In other words, this appears to be another example of the benefits reported in this connection during the past generation as a result of a number of different, non-specific agents, both chemical and biological, which have been advanced and later either gradually discarded or reserved for special, limited use. It seems to the writers, therefore, that while under certain conditions such as those enumerated, patients may recover because of the benefit conferred by the drugs, the more general rule may eventually be accepted that the sulfonamide derivatives are not strikingly effective in checking the majority of *genuine* staphylococcal septicemias.

Summary and Conclusions

1. A large number of patients (62) with staphylococcal septicemia, referred for possible serum therapy, had previously been under sulfonamide treatment.

2. Of these, 18 were given sulfanilamide, 12 sulfapyridine, 2 sulfamethylthiazole, 20 sulfathiazole, and 10 combinations of the different compounds.

3. In all these patients, the evidence suggests that the drugs failed to suppress the infection.

4. Of the 62 patients, however, 20 eventually survived, presumably because of other treatment. If this number be disallowed as discussed above, the mortality rate is still 67 per cent or approximately the usual average in such infections.

5. It is realized, however, that successfully treated patients were not referred to the writers, so that this report makes no pretense at statistical validity.

6. Under special conditions, which are enumerated, it may be that the sulfonamides have a certain value in staphylococcal septicemia, but such examples are probably in the minority.

7. In support of the above opinion is the in vitro observation that sodium sulfathiazole in concentrations as high as 30 per cent, which is effective in sterilizing completely heavy growths of *B. coli* in less than 15 minutes, has little if any restraining influence on different strains of *Staphylococcus*, even after one hour exposure.

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THE VALUE OF STERNAL MARROW ASPIRATION AS A METHOD OF BONE MARROW BIOPSY *

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The purpose of this paper is to attempt an evaluation of the method of aspirating portions of the sternal marrow through a needle or a small canula for study of the marrow cells. The assumption is that by this procedure a fair sample of the cellular components of the organ known as bone marrow can be obtained. Since Arinkin [1] first described this method in 1929, it has been widely used and has been the subject of a number of excellent papers. Some authors [2, 3, 4, 5, 6] found the procedure satisfactory for study of the marrow. Others [7, 8] apparently experienced difficulty in obtaining representative specimens of marrow and believed that aspiration specimens lack the fundamental architectural arrangement of the marrow without which the cellular relations can not be evaluated properly. They recommended instead the trephine operation. We do not attempt in this report to review the extensive literature concerning bone marrow biopsy; we merely record our experiences and comment on the specimens of aspirated sternal marrow studied, in an effort to evaluate the usefulness of this method of biopsy.

We employed the following technic. The skin over the upper sternum is painted with tincture of iodine and 2 per cent procaine hydrochloride is used as local anesthetic. A No. 16 lumbar puncture needle with a stilette, fashioned as shown in figure 1, is inserted into the outer table of the midsternum just below the junction of the manubrium and gladiolus. The ridge of this junction is easily identified, and with moderate pressure and a screwing motion the outer table can be perforated. A crunching sound indicates that the marrow cavity has been reached. The first suction pressure with a 5 c.c. Luer syringe frequently draws no marrow and it may be necessary to insert the stilette in order to remove a small plug of tissue or bone in the end of the needle. A few trials with gentle suction pressure may be necessary before the marrow is sufficiently liberated from the marrow spaces to appear in the syringe. About 0.2 to 0.3 c.c. of marrow is withdrawn. Spreads are made directly from the end of the needle. Drops of marrow are deposited on a cover glass, a second cover glass is placed over the drop so that the film spreads by capillary attraction. These films are stained with the Jenner-Giemsa stain.

With each set of cover glass films, a few prepared with 2 per cent cresyl blue were drawn in order to facilitate the study of reticulocytes in the mar-

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row. Differential counts were made on each specimen of marrow on the basis of 500 to 1000 cells counted. Each author checked the count of the other and if essential differences occurred the average was selected. Disagreement on the type of cell, which occurred occasionally, was settled by further study, consultation and reference to Osgood's atlas of the blood cells. Our material comprised 180 marrow preparations which constitute the chief data of this paper. Because of the simplicity of its classification, we used

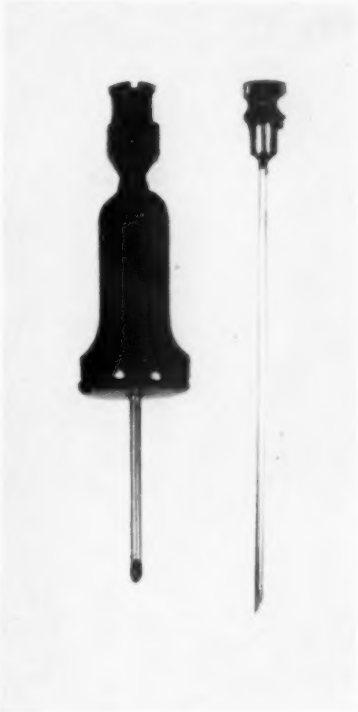

FIG. 1.

Arinkin's normal values (table 1). We believe, however, Segerdahl's figures for normal values (table 2) may be more reliable and accurate as they are based on cell counts of the marrow in 50 normal males from 20 to 30 years of age, 40 females in the same age group and 18 persons over 65 years of age. We learned from Segerdahl personally that her "Reticulumzellen" are identical with our clasmatocytes, a cell type which we have added to Arinkin's table. We have been much interested in the cell often referred to as—hematogone, a primitive cell resembling a lymphocyte but showing a very small rim of basophilic cytoplasm in which no granules are seen by ordinary staining. The nucleus shows a densely matted chromatin. We can not with confidence differentiate this cell from the lymphocyte.

TABLE I

Normal Values According to Arinkin (Modified)

Cell Types	Per Cent
Myeloblasts	1.0 – 2.4
Promyelocytes	1.0 – 2.8
Myelocytes	
Neutrophilic	4.5 – 8.6
Eosinophilic	0.3 – 1.0
Metamyelocytes	1.4 – 3.4
Eosinophilic	0.3 – 1.0
Polymorphonuclears	
Neutrophilic	41.0 –55.0
Eosinophilic	0.6 – 4.0
Basophilic	0.0 – 1.0
Lymphocytes	7.3 –16.5
Plasma cells	0.3 – 0.9
Megakaryocytes	0.6 – 6.1
Monocytic cells	2.1 – 9.3
Pro-erythroblasts (including macroblasts)	0.8 – 2.9
Erythroblasts (including normoblasts)	5.7 –16.0
Clasmatocytes	0.03– 0.3

TABLE II

Normal Values According to Segerdahl *

Cell Types	Group 1 (50 men)		Group 2 (40 women)		Group 3 (18 old persons)	
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
Myeloblasts	1.32	0.57	1.20	0.53	1.23	0.70
Promyelocytes	1.35	0.76	1.65	0.58	1.62	1.01
Neutrophilic myelocytes	15.00	3.76	16.58	2.61	11.14	4.72
Eosinophilic myelocytes	1.37	0.63	1.45	0.83	1.17	1.20
Neutrophilic metamyelocytes	15.69	3.22	15.82	2.39	12.76	5.17
Neutrophilic stab/band forms	10.48	3.73	8.26	2.09	6.07	2.88
Neutrophilic polymorphonuclears	20.86	5.47	21.66	5.20	24.32	9.06
Eosinophilic polymorphonuclears	1.44	0.77	1.55	1.26	2.08	1.83
Basophilic polymorphonuclears	0.14	0.12	0.16	0.15	0.23	0.21
Monocytes	2.27	0.89	1.61	0.71	2.66	1.58
Lymphocytes	16.76	4.77	18.09	3.81	23.64	9.17
Erythroblastic series (all nucleated red cells)	12.88	4.39	11.50	3.22	12.37	6.20
Histiocytes ("Reticulumzellen")	0.03	0.07	0.05	0.08	0.09	0.11
Megakaryocytes	0.03	0.05	0.02	0.05	0.05	0.09
Plasma cells	0.39	0.35	0.42	0.23	0.55	0.56

* Adapted from Segerdahl,[2] Table 4, p. 66.

Table 3 shows the results of studies on aspirated sternal marrow in 135 patients, with respect to diagnostic aid or confirmation of diagnosis gained through the procedure. The patients were grouped under the final clinical and laboratory diagnosis in each case. It is interesting to note that the diagnosis arrived at after thorough study of the case before sternal marrow aspiration was rarely changed by the data subsequently obtained through the study of the marrow cells. In 13 cases, aspirated sternal marrow and mar-

row preparations obtained by the trephine method were compared. In only one of these were significantly superior preparations as to number, type and distribution of cells obtained by the trephine method. This was a case of extensive arterial occlusion with thrombocytosis in which study of the number and distribution of megakaryocytes in the marrow was facilitated by the trephine preparations (figures 2 and 3). The marrow aspiration films

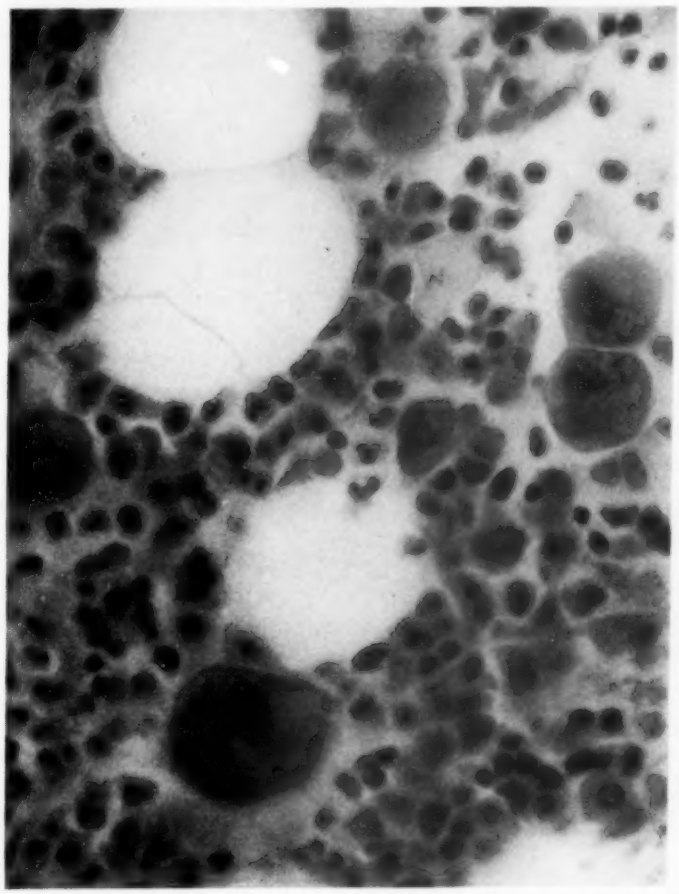

FIG. 2. From patient with thrombocythemia. Increased number and distribution of megakaryocytes. (Trephine biopsy.)

showed striking instances of megakaryocytes surrounded by huge agminations of platelets (figure 3). This picture was not seen in the films of marrow obtained by the trephine method. We studied sections from fixed tissue preparations of marrow obtained by the trephine method in only three of the 12 cases. Custer and others [7, 8] have ascertained that study of such preparations is of great value. These preparations particularly show the changes in the architecture of the marrow and carry diagnostic implications

which would be missed in films of aspirated marrow. One case from the Hodgkin's group, which is reviewed on page 455, illustrates this point.

An analysis of table 3 according to groups shows that sternal marrow studies of the cases of subleukemic (aleukemic) and monocytic leukemia and of plasmacytoma gave definite information helpful in diagnosis and prognosis. Lymphatic and myelogenous leukemia can usually be readily identified without differential marrow cell counts. The captions, "aid to

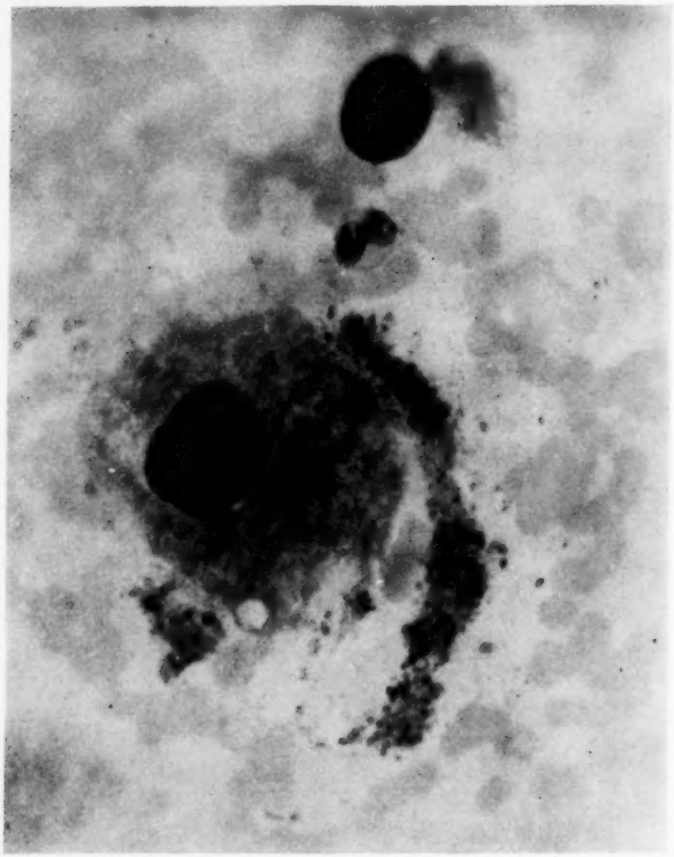

FIG. 3. Patient with thrombocythemia. Megakaryocytes shown in aspirated marrow.

diagnosis" and "confirmation of diagnosis" require clarification. By "aid to diagnosis" we mean that the percentage or the myeloid-erythroid ratio of certain types of marrow cells, or both together, gave added information indicative of some definite lesion or recognized type of dysfunction of the hematopoietic system. "Confirmation of diagnosis" indicates that marrow studies narrow the field of diagnostic possibilities by ruling out or ruling in suspected alterations in marrow function or morphology; thus they confirm the original diagnosis. Such evidence may be purely negative.

TABLE III

Grouping of Cases According to Diagnosis

Diagnosis	Number of Cases	Number of Marrow Specimens Studied	Abundant Cellular Material	Inadequate Cellular Material	Aid to Diagnosis	No Aid to Diagnosis	Confirmation of Diagnosis	Trephine and Aspiration Used	Diagnosis by Marrow Study
Leukemia									
Lymphatic	18	28	28		18		18		
Myelogenous	10	15	15		10		10		
Subleukemic acute	3	3	3		3		1		2
Monocytic	7	11	11		7		5		2
Multiple myeloma	7	9	9		6		6	1	1
Anemia									
Hypochromic	10	10	8	2	8	2	8		
Pernicious	10	13	13		10		10		1
Hyperchromic	4	6	6		4		4		1
Aplastic	8	14	14				3	3	1
of Carcinoma	3	3	3		3		3	1	1
Hemolytic anemia									
Icteric type, acquired	2	3	3		2		2		
Familial	1	2	2		1		1		
Purpura, thrombocytopenic	5	5	5		0	5	5	1	
Polycythemia vera	8	10	10		0	6	0	1	
Chronic leukopenia with neutropenia	5	5	5		0	5	0		
Chronic infections (2 cases of bacterial endocarditis)	7	7	7		1	6	2		1 (marrow culture)
Agranulocytosis	2	2	2		2		2		
Boeck's sarcoid	3	3	3		0	3	0	1	
Thrombocythemia associated with arterial disease	1	4	4		1		1	1	
Leukemoid reaction	3	3	3		3		3		
Lymphoma									
Hodgkin's	14	20	20		1	10	4	4	1
Lymphosarcoma	4	4	4		0	4	0		
Total	135	180	178	2	80	41	88	13	11

The anemias have not been thoroughly studied. However, in cases of hypochromic anemia very little information was obtained by sternal puncture. In the sternal marrow of pernicious anemia the presence of megaloblasts, especially in untreated patients, practically established the diagnosis. In one patient with a clinical and laboratory diagnosis of pernicious anemia, roentgenograms of the spine showed extensive demineralization and a compression fracture of the second lumbar vertebra. The sternal marrow was examined at intervals of four days after institution of parenteral liver therapy. An

initial sternal puncture had been secured before treatment was begun. The curve of maturation of the erythropoietic elements was used to test the response to therapy and it was paralleled exactly by the behavior of the cellular elements of the peripheral blood. In a patient with prostatic hypertrophy, urinary obstruction and infection, operation was postponed because of the accompanying anemia. Investigation showed a macrocytic hyperchromic anemia. No free hydrochloric acid appeared after histamine administration. The differential marrow cell count revealed a low myeloid-erythroid ratio with 11 per cent megaloblasts—an indication of pernicious anemia. The patient was placed on optimal doses of parenteral liver extract (Lederle, 1 c.c. = 15 units). After two weeks the reticulocytes had not risen significantly and during the last days of the trial treatment from 20 to 24 per cent of monocytes in mature and immature forms appeared in the marrow; a few also appeared in the peripheral blood. Roentgenograms of the skeleton showed no metastases or other lesions. The working diagnosis was changed to subleukemic monocytic leukemia or aplastic anemia.

In the hyperchromic anemias other than Addison's, the aspiration method was of value chiefly in differential diagnosis. In one patient with malnutrition and avitaminosis following prolonged diarrhea and vomiting, the sternal marrow so closely resembled that found in pernicious anemia that differentiation was possible only after failure of response to liver therapy and after spontaneous return of the marrow to a normal pattern when a proper state of nutrition had been restored. The eight cases of aplastic anemia presented distinctly cellular marrows. In each case the marrow presented certain individual variations not found in the others. They could be divided into the two groups described by Rhoads and Miller.[9] Their Group 2, aplastic anemia with hyperplastic marrow, would include four of our cases, and their Group 3, aplastic anemia with active marrow, would include the remaining four. The marrows of our patients of the Group 2 type showed a high percentage of primitive cells and in this respect suggested subleukemic leukemia. The marrows of our patients of the Group 3 type more nearly resembled the marrow picture of pernicious anemia. In two of these patients aplastic anemia had developed following administration of the arsphenamines. Two of our patients with aplastic anemia had 6 to 10 per cent plasma cells in the marrow. One of these also had as high as 15 per cent monocytes in the peripheral blood but the marrow showed only 1 to 2 per cent of these cells. One patient, a young woman 22 years of age, had the typical findings of aplastic anemia in her peripheral blood with marked decrease of hemoglobin and of all the cellular elements of the blood. She had been kept alive for over a year by transfusions. Examination of her sternal marrow revealed an active marrow, especially in erythroid elements. Splenectomy was done whereupon the peripheral blood gradually returned to normal. For several months there was only slight change in the differential marrow cell count except that the megakaryocytes were increased and the

platelets markedly increased. This finding suggests that the spleen in some manner inhibited the delivery of cells to the peripheral circulation.

The few observations made in cases of hemolytic anemia showed no noteworthy changes in the marrow except for active erythropoiesis. The same may be said of the cases in the polycythemia vera and thrombocytopenic purpura groups. The latter showed very few platelets in the marrow. In one patient megakaryocytes were increased which in this instance proved to be a favorable prognostic sign. In the two patients with agranulocytosis the maturation of the marrow was arrested at the level of the early myeloid elements. There was nothing characteristic in the marrows of the group with chronic infections. One of the patients in this group, a woman 52 years of age, had the clinical characteristics of subacute bacterial endocarditis. She was weak, pale, had a swing of two to three degrees in daily temperature, had a rough presystolic murmur leading up to the first sound and a history of a former cardiac lesion. Her spleen was barely palpable on deep inspiration. Four blood cultures from venous blood taken during her hospitalization were negative. Sternal marrow aspiration was done and at the same time 10 c.c. of blood were withdrawn from the right median basilic vein. Both blood and marrow specimens were placed in brain broth media and incubated. The blood culture was negative; the marrow culture yielded an organism of the *Streptococcus viridans* type. Later in the course of the disease blood cultures yielded an organism of similar type. The marrow in Boeck's sarcoid yielded no contributory information as to diagnosis. In one patient in whom both the aspiration and the trephine methods of biopsy were used, the former showed a myeloid-erythroid ratio of 1:7.8 and the latter, 2:7.6. The specimen obtained by the trephine method yielded the lesser number of erythroblastic elements.

The lymphoma group, including Hodgkin's disease and lymphosarcoma, and the leukemoid group constituted an interesting study. Certain patients in these groups showed metastatic extension in one or more portions of the osseous system with evident marrow irritation. We have noted especially in Hodgkin's disease that a high white blood cell count (above 20,000 cells per cubic millimeter) with a myeloid reaction usually indicates skeletal involvement associated with either marrow metastases or irritation of the marrow. The sternal marrows in this group in some instances showed a leukemoid or myeloid reaction difficult to distinguish from the early myeloid reaction of myelogenous leukemia. A distinguishing point appears to be a lower myeloid-erythroid ratio than is found in leukemia (see table 4). The megakaryocytes were not increased in the marrows of the patients with Hodgkin's disease and lymphosarcoma; the percentage varied from 0.2 to 2 while in the majority of the patients with Hodgkin's disease it was 0.2 per cent. The marrow specimen of a patient with lymphosarcoma showed many megakaryocytes (figure 4) in a thick portion of the smear. This patient had

extensive metastatic involvement of the spine and 53,000 white blood cells—findings which indicate marrow as well as bone involvement.

Table 4 gives a graphic representation of the myeloid-erythroid ratio of some of the groups discussed in connection with table 3. It has no importance aside from indicating a certain trend of the ratio in some of the

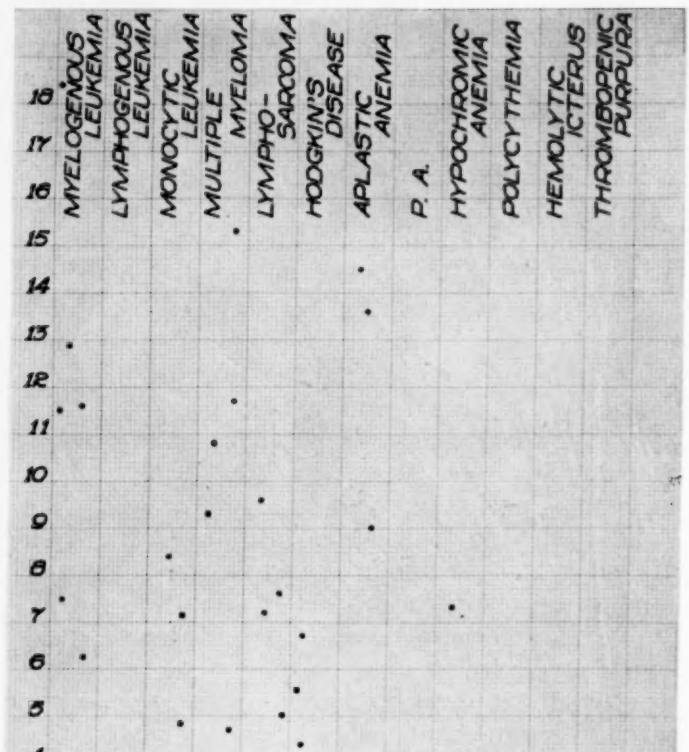

TABLE 4. Myeloid-Erythroid ratio—Each dot represents the figure obtained by dividing the myeloid by the erythroid elements.

groups, while in other groups, such as the Hodgkin's group, the ratio shows a scatter.

The case reports which follow illustrate the limitations as well as the usefulness of sternal marrow studies as an aid in diagnosis and prognosis of blood dyscrasias.

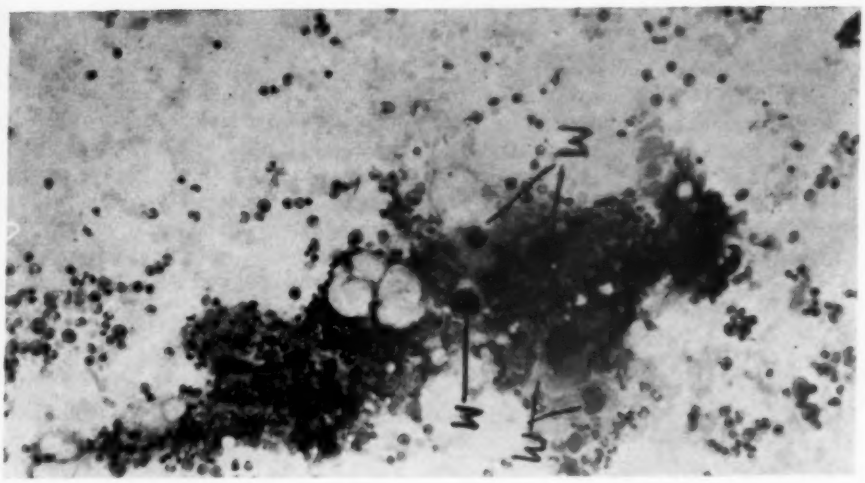

FIG. 4. Increased number of megakaryocytes in marrow of patient with lymphosarcoma.

CASE REPORTS

Case 1. An Italian man, aged 54, complained of weakness, fever and "night sweats." On August 26, 1940, hemoglobin was 56 per cent, red blood cells 3,700,000, white blood cells 5,700 with lymphocytes 44 per cent and monocytes 14 per cent. The liver and spleen were greatly enlarged. Diagnosis of brucellosis was tentatively excluded by negative agglutination and phagocytic index tests. According to the history the lymph nodes in the left cervical triangles had been somewhat enlarged but had been reduced to normal size after a few roentgen-ray treatments. Differential diagnosis of Hodgkin's disease, Banti's disease or subleukemic leukemia was considered. The sternal marrow obtained by aspiration showed a myeloid-erythroid ratio of 46.6 : 34.8. No maturation arrest of myeloid elements was apparent at an early level of maturity but a certain amount of fibrous tissue was noted in the films. A trephine specimen of marrow showed, after fixation, an architectural arrangement of areas of active marrow with scattered areas of considerable fibrosis. Later biopsy specimen of a lymph node revealed the histologic picture of Hodgkin's disease. Splenic puncture did not contribute to diagnosis. Roentgen treatment decreased the size of the liver and spleen but ascites appeared and the patient failed rapidly.

Case 2. A woman 67 years of age had a "swelling in the right breast" in which the whole breast became involved. Examination of the blood revealed a white cell count of 40,000 with an increased percentage of lymphocytes. There were enlarged lymph nodes in the right axilla. The hardness and nodular character of the mass in the breast suggested a carcinoma. The question at issue was whether the blood picture could be explained on basis of the breast lesion. The sternal marrow revealed 8.4 per cent lymphoblasts and 65.2 per cent lymphocytes. Biopsy of an axillary node revealed carcinomatous metastases into a node which showed the histological pattern of lymphogenous leukemia.

Case 3. A man, aged 57, had enlarged, matted nodes in the left anterior cervical triangle. The spleen was palpable. Red blood cells and hemoglobin were normal. White blood cells numbered 7,200 of which 57 per cent were polymorphonuclear cells, 23 per cent lymphocytes and 20 per cent monocytes. Biopsy of one of the cervical lymph nodes was diagnosed "malignant lymphoma, stem cell type, probably monocytic leukemia." The sternal marrow showed a moderate myeloid hyperplasia with 8 per

cent lymphocytes and only 2 per cent monocytes. A diagnosis of Hodgkin's disease was made on the basis of the marrow findings. The subsequent course of the disease confirmed this diagnosis.

Case 4. In November 1937 a woman, aged 59, was studied because of failure to respond to parenteral liver extract, after a diagnosis of pernicious anemia had been made. She showed a smooth, glistening tongue, she had no free hydrochloric acid in the gastric contents after histamine, her cervical and axillary lymph nodes were palpable and her liver and spleen were enlarged. Red blood cells were 2,800,000, hemoglobin 58 per cent and white blood cells 5,700 with 52 per cent lymphocytes which later rose to 74 per cent of a total white blood count of 5,250 cells. Sternal marrow showed 20 per cent lymphocytes and a moderate increase of myeloid cells. A tentative diagnosis of early lymphatic leukemia was made. After following the patient for over three years during which time the hematologic findings remained about the same, the diagnosis was changed to Hodgkin's disease. We are awaiting the patient's permission to do a biopsy of a lymph node.

Case 5. This patient, a young Italian girl aged 17, was seen in consultation because of a severe reaction following a blood transfusion during which the temperature rose to 107° F. About three months previously she had been admitted to a hospital because of marked prostration, fever and anemia. Her white blood cell count had been 2000, with only about 20 per cent polymorphonuclear cells. A diagnosis of agranulocytosis had been made and two transfusions had been given with apparent benefit. Upon her return home the anemia and leukopenia persisted. When she was readmitted to the hospital the day before the severe transfusion reaction, her white blood cell count was 800 per cubic millimeter. One of the stained blood films made during hospitalization was reëxamined and cells that had been classified as peculiar lymphocytes were recognized as monocytes. A bone marrow examination revealed 8 per cent monoblasts and 47.4 per cent monocytes. The patient died five days after the transfusion reaction. The obvious diagnosis was subleukemic monocytic leukemia.

Case 6. A woman, aged 62, was seen in consultation because of an unexplained severe anemia associated with marked prostration and palpable lymph nodes in the submaxillary region. The results of previous thorough laboratory and clinical studies had been negative with the exception of the white blood cell count which ranged from 10,000 to 15,000 and showed from 20 to 42 per cent monocytes. Three sternal marrow aspirations taken at intervals showed monocytes up to 24 per cent and monoblasts up to 12 per cent. A diagnosis of monocytic leukemia was made.

Case 7. A man, aged 78 years, had been under treatment in a sanatorium for three months because of unexplained severe anemia. When he was seen at home (he had been dismissed from the sanatorium in a state thought to be terminal, with marked emaciation, prostration and delirium) his red blood cells were 1,900,000, hemoglobin 38 per cent, white blood cells 4,000 with 49 per cent polymorphonuclears, 49 per cent lymphocytes and 1 per cent each of eosinophiles and monocytes. Sternal aspiration was at that time not permitted by the family. The patient was admitted to the hospital because he had sustained a fracture of the left hip. At that time roentgenograms showed a pathologic fracture of the upper portion of the femur apparently due to a metastatic malignant lesion. The sternal marrow revealed 25 per cent proplasmacytes and 18 per cent plasmacytes. A diagnosis of plasmacytoma (multiple myeloma) was made and substantiated by findings at autopsy.

Case 8. A man, aged 65, who come under observation in 1936, had all the criteria necessary for a diagnosis of pernicious anemia except that a small amount of free hydrochloric acid was found in the gastric secretions. His reticulocyte response to parenteral liver extract was not satisfactory but his red blood cells and hemoglobin rose nearly to normal levels during three months of this treatment. They then slowly fell and the white blood cells decreased from 2,800 to 1,500 with from 80 to 94 per cent lymphocytes. Aspirated marrow films showed marked hyperplasia of the marrow,

particularly of the erythropoietic elements. In 1937 the patient returned to his home in Boston. He was again hospitalized and a complete examination, including bone marrow biopsy, was made. He showed no response to a long course of therapy with liver given parenterally and raw liver juice given by mouth. Transfusions administered during 1938 and 1939 resulted in only temporary improvement. The white blood cells fell to 900, marrow biopsy done on January 25, 1939, showed "hypoplasia." Diagnosis was aplastic anemia.

Case 9. A man, aged 63, with marked anemia had a normal white blood cell count with 2 per cent each of myelocytes and metamyelocytes. Extensive spotty osteoporosis of the rib cage and the pelvic bones was considered to be due to carcinomatous metastases. Marrow aspirated from the sternum (figure 5) showed a few clusters of carcinomatous cells. Fixed tissue smears from the marrow obtained by the trephine method showed definite metastatic carcinoma.

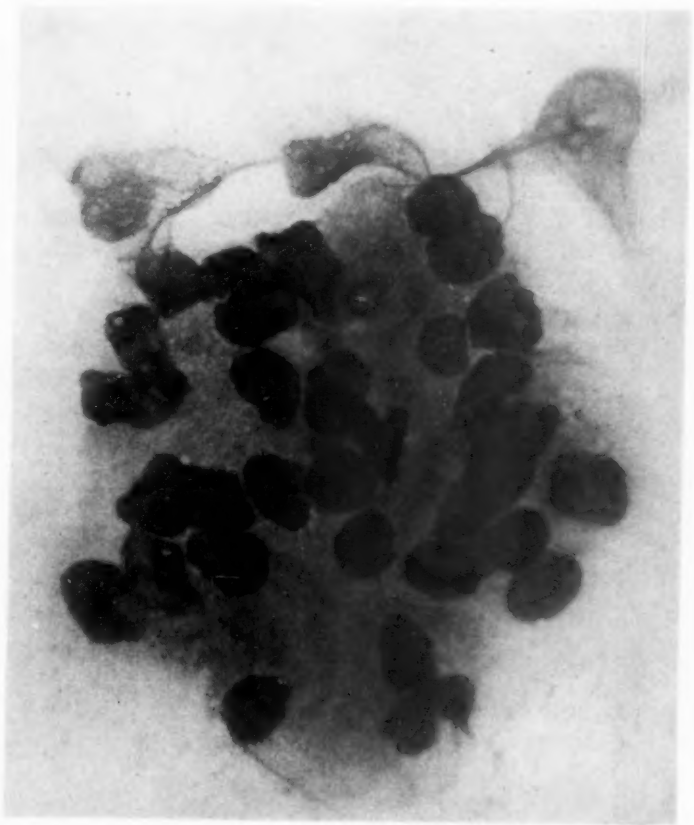

FIG. 5. Aspirated marrow showing cluster of carcinoma cells in patients with bone metastases.

SUMMARY

In our experience sternal aspiration has been satisfactory as a method of marrow biopsy. It is easy to perform and does not cause any particular discomfort to the patient. We have seldom failed to get a fair sample of

the sternal marrow. Our technic has improved especially during the past year as a result of accumulated experience. The question of the diagnostic value of aspirated marrow specimens is largely one of individual opinion and experience. Obviously this method should not be used to supplant or short-cut other recognized diagnostic procedures, as our knowledge of the specific information gained from marrow studies is as yet rather limited. Sternal marrow aspiration should be employed as a means of gaining information regarding the morphology of the marrow cells as well as their respective number in diseases involving the hemopoietic system. Such information should always be interpreted in the light of all other data at our disposal. When used in this manner with recognition of its limitations, the method has proved in our experience a distinct help. The trephine method should be used whenever the aspiration method appears inadequate.

An interesting field for further investigation is the study of the marrow in certain chronic infections, such as brucellosis and bacterial endocarditis. The method of marrow aspiration is particularly applicable to investigative studies of this type. We are using marrow cell counts as one means of checking results of therapy in several patients and hope to report useful data after sufficient observations have been made.

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CHANGES IN THE CARDIAC SHADOW FOLLOWING PHARMACOLOGICAL "SHOCK" THERAPY OF SCHIZOPHRENIA *

By HAROLD W. STERLING, M.D., *Little Rock, Arkansas,* and CRAWFORD N. BAGANZ, M.D., *Lyons, New Jersey*

STUDIES of the heart following pharmacological shock therapy have been the object of many research projects. Farrell and Vassaf [1] reported changes in seven-foot teleoroentgenograms of the heart before, during, and after the insulin treatment of schizophrenia. In five of the six cases treated "there occurred a measurable enlargement of the cardiac shadow. . . ." These authorities also reported that "measurements of the heart were made at various intervals after the cessation of treatment; these showed reduction in the heart shadow to a size approaching that prior to treatment and coincidently it was observed that the favorable therapeutic effects at the end of treatment failed to be maintained." They further suggested "that some of the mental improvement and cardiovascular changes associated with insulin shock therapy may be explained by stimulation of the sympathetic nervous system. It appears that when the therapeutic stimulation of the sympathetic system ceased, its favorable effects on the mental condition and on the cardiovascular system of the patient gradually subsided."

That insulin is of value in the treatment of malnutrition and that the utilization of insulin in large doses in "shock" therapy causes a marked gain in weight, are such commonplace observations as to verge upon triteness. Elementary physiological knowledge coupled with the daily experience of roentgenologists clearly demonstrates that with an increase of the intra-abdominal contents there is a concomitant rise of the diaphragm. This knowledge and experience further demonstrate that the rise of the diaphragm is accompanied by a marked change of the cardiac shadow, apparently due to rotation of the heart about a vertical axis. That there is a close relation between the height of the diaphragm and the size of the cardiac shadow is not new or original as the work of Chandlee and Burvill-Holmes [2] will certify. However, this fact has been commonly overlooked and frequently the only practical guide employed in estimation of the cardiac size has been the cardiothoracic ratio.

Field, in his studies of vitamin B_1, as displayed by the Upjohn Laboratories in their advertisements of the same,[3] showed reproductions of teleroentgenograms with marked changes in the contour of the heart shadow and an accompanying change in the height of the diaphragm. The changes

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in the height of the diaphragm are not mentioned as contributing factors to the change in the cardiac shadow.

Messinger [4] in his study of the effects of insulin shock therapy on the heart, excluded from his studies those cases in which teleoroentgenograms revealed an appreciable difference in the height of the diaphragm. As the authors believe that this factor is most important in determining cardiac contour, this paper concerns itself principally with an attempt to correlate this factor with differences in total diameter of the cardiac shadow.

Nineteen patients who had received insulin " shock " therapy for schizophrenia were studied for changes in cardiac outline. (Table 1 and figure 1.)

TABLE I

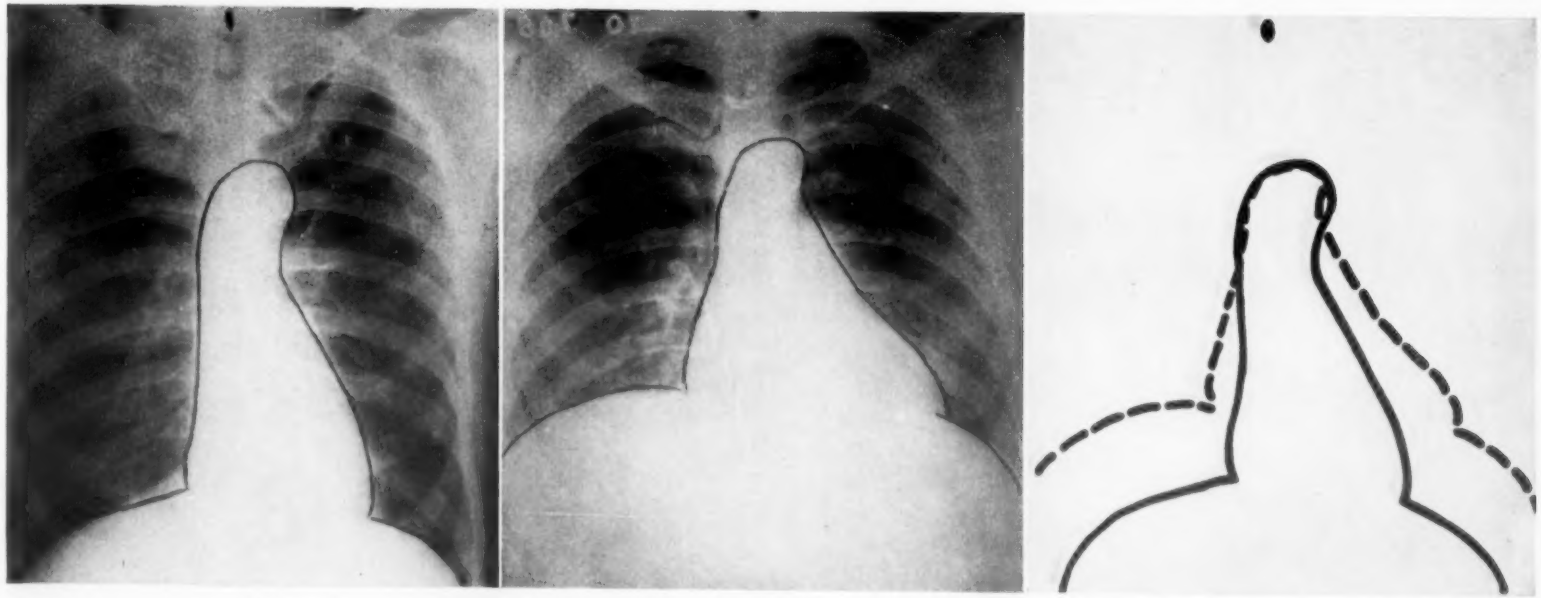
Correlation of Changes in Cardiac Shadow with Changes in Height of Diaphragm in Cases That Received Pharmacological "Shock" Therapy

	Before Treatment		After Treatment	
	Height of Diaphragm*	Total Trans. Diam. Heart (cm.)	Height of Diaphragm*	Total Trans. Diam. Heart (cm.)
Case 1	21.8 cm.	12.3 cm.	20.4 cm.	13.0 cm.
Case 2	21.5 cm.	13.0 cm.	19.9 cm.	15.4 cm.
Case 3	30.2 cm.	10.9 cm.	27.5 cm.	12.0 cm.
Case 4	25.2 cm.	11.5 cm.	22.7 cm.	12.4 cm.
Case 5	24.0 cm.	13.8 cm.	22.3 cm.	14.6 cm.
Case 6	26.4 cm.	11.6 cm.	23.5 cm.	12.8 cm.
Case 7	24.3 cm.	13.4 cm.	24.0 cm.	13.8 cm.
Case 8	24.0 cm.	12.5 cm.	24.0 cm.	12.7 cm.
Case 9	25.1 cm.	11.7 cm.	20.2 cm.	14.6 cm.
Case 10	27.2 cm.	12.0 cm.	25.3 cm.	13.3 cm.
Case 11	25.0 cm.	10.6 cm.	23.5 cm.	11.7 cm.
Case 12	25.8 cm.	11.4 cm.	24.4 cm.	14.5 cm.
Case 13	20.6 cm.	12.0 cm.	21.0 cm.	12.3 cm.
Case 14	28.3 cm.	12.0 cm.	23.0 cm.	15.0 cm.
Case 15	25.8 cm.	12.2 cm.	25.5 cm.	12.3 cm.
Case 16	26.8 cm.	10.4 cm.	21.6 cm.	15.0 cm.
Case 17	27.5 cm.	11.2 cm.	26.0 cm.	13.1 cm.
Case 18	26.5 cm.	11.2 cm.	26.5 cm.	11.2 cm.
Case 19	22.0 cm.	14.0 cm.	20.2 cm.	14.0 cm.

* Height of diaphragm is expressed in centimeters from spinous process of first dorsal vertebra to dome of diaphragm, during deep inspiration.

These patients had one or more six-foot teleoroentgenograms of the heart prior to insulin therapy and one or more following the treatment. In addition to these 19 patients, there were three others who received insulin in subshock doses for treatment of malnutrition and who underwent marked gains in weight but who did not experience hypoglycemic coma. These three patients served as valuable controls and clearly demonstrated that changes in cardiac contour could take place without organic heart disease being present. All patients were free from cardiac disorders prior to and following therapy.

The accompanying chart (table 2 and figure 2) shows the diaphragmatic changes, and changes in total diameter of the cardiac shadow at dif-



(*a*) (*b*) (*c*)

FIG. 1. Reproduction of teleoroentgenograms of case 16: (*a*) before insulin therapy, (*b*) after insulin therapy, (*c*) "a" superimposed upon "b" with spinous process of first dorsal vertebra at same level. Diaphragm, cardiac outline and spinous process of first dorsal vertebrae have been retouched for greater contrast.

TABLE II

Correlation of Changes in Cardiac Shadow with Changes in Height of Diaphragm in Cases That Received Sub-Shock Doses of Insulin for Treatment of Malnutrition

	Before Treatment		After Treatment	
	Height of Diaphragm*	Total Trans. Diam. Heart (cm.)	Height of Diaphragm*	Total Trans. Diam. Heart (cm.)
Case 20	26.5 cm.	10.8 cm.	21.0 cm.	12.4 cm.
Case 21	24.0 cm.	11.1 cm.	21.0 cm.	13.8 cm.
Case 22	26.0 cm.	10.6 cm.	25.0 cm.	11.3 cm.

* Height of diaphragm is expressed in centimeters from spinous process of first dorsal vertebra to dome of diaphragm, during deep inspiration.

ferent stages of nutrition. Inasmuch as some authorities feel the cardiac changes described may have been of organic heart disease resulting from "shock" therapy, it is interesting to note that the three cases treated for malnutrition had the same changes in diaphragm and cardiac contours as the cases that underwent hypoglycemic coma. It is also worthy of notice that when one of these individuals who had been treated for malnutrition was removed from adequate dietary supervision and removed from sub-shock doses of insulin, he underwent a loss of weight almost to his previous level. Accompanying this relapse to his former weight was a return to a practically identical cardiac shadow and a lowering of the diaphragm to the former level.

Farrell and Vassaf noted a return of the previous cardiac shadow when insulin treated patients underwent a psychiatric relapse. The authors concur with the opinion of other workers in the field of pharmacological "shock" therapy that one of the first signs of an impending relapse is a marked loss of weight. Therefore, we believe that the weight loss of these relapsed patients and the change in cardiac contour have the relation of cause and effect, and further that this change is symptomatic of a relapse rather than serving as an etiological factor, as suggested by Farrell and Vassaf.

SUMMARY

The authors have observed in the course of pharmacological "shock" therapy a change in the cardiac contour. It was first found that this change was an increase in total tranverse diameter of the heart and that this increase roughly paralleled a gain in weight.

Further studies revealed a close correlation between the change in the height of the diaphragm and a change in the total transverse diameter of the heart.

The authors report three cases in which insulin in sub-shock doses was given for malnutrition and in which very similar changes were noted to those taking place in the cases receiving large "shock" doses of insulin.

(a) (b) (c)

FIG. 2. Reproduction of teleoroentgenograms of case 20: (*a*) before insulin therapy, (*b*) after insulin therapy, (*c*) "a" superimposed upon "b" with spinous process of first dorsal vertebra at same level. Diaphragm, cardiac outline and spinous process of first dorsal vertebrae have been retouched for greater contrast.

Conclusion

It is the opinion of the authors that insufficient importance has been attached to the height of the diaphragm as one of the factors influencing the total transverse diameter of the heart as seen on a teleroentgenogram.

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ELECTROCARDIOGRAPHIC CHANGES IN STAB AND GUNSHOT WOUNDS OF THE HEART, WITH REVIEW OF THE LITERATURE*

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Since the dawn of the twentieth century, many hundreds of stab and gunshot wounds of the heart in human beings have been treated surgically, but not until 1924 was a case with serial electrocardiographic tracings recorded.[1] Heart wounds are still sufficiently novel that individual or multiple case reports continue to be published, but few of these contain complete electrocardiographic studies. It would seem that such studies might offer a method of determining electrocardiographic changes produced by localized injury to different portions of the human heart.

A patient with a stab wound of the left ventricle, who had repeated tracings made, has been observed at this hospital. The changes noted were suggestive of pericarditis, and no evidence of a localized lesion of the myocardium could be found. Koucky and Milles [2] collected nine cases of stab wounds of the ventricles and added one of their own. They concluded "that the electrocardiographic changes noted are, as is the generally accepted opinion, purely myocardial in origin and are dependent on the degenerative changes that occur in the muscle fibers involved." On the other hand VanderVeer and Norris,[3] who reviewed several recorded stab wounds of the heart, and added a case with traumatic laceration of the right auricle, stated: "The progressive electrocardiographic changes in many cases of stab wound of the ventricle suggest acute pericarditis rather than a single anterior lesion of the myocardium." Our interest was stimulated by this divergence of opinion to review the cases with tracings that had been published. Those which had abnormalities due to injury of some specialized tissue, such as the bundle of His, were not considered.

That an inflammatory reaction of the pericardium is an almost universal complication of penetrating injuries of the heart has been recognized for many years. Hesse,[4] on the basis of a review of the after-results of 12 cases of his own and 107 cases from the literature, stated that the appearance of a dry pericarditis after heart suture could almost be considered a rule. If not reported, it was probably due to failure on the part of the surgeon to observe it. Beck [5] mentions the high incidence of a postoperative pericardial effusion and subsequent pericardial adhesions. The likelihood of these complications is apparent when it is considered that the traumatizing agent intro-

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duced is contaminated with bacteria, that there is free blood present in the pericardial sac, generally undue haste in the emergency operation, and that there is considerable manipulation of the heart incident to the operative intervention. In dogs Barnes and Mann [6] have shown that mere opening of the pericardium resulted in extensive pericarditis. This was confirmed by Fowler, Rathe and Smith.[7]

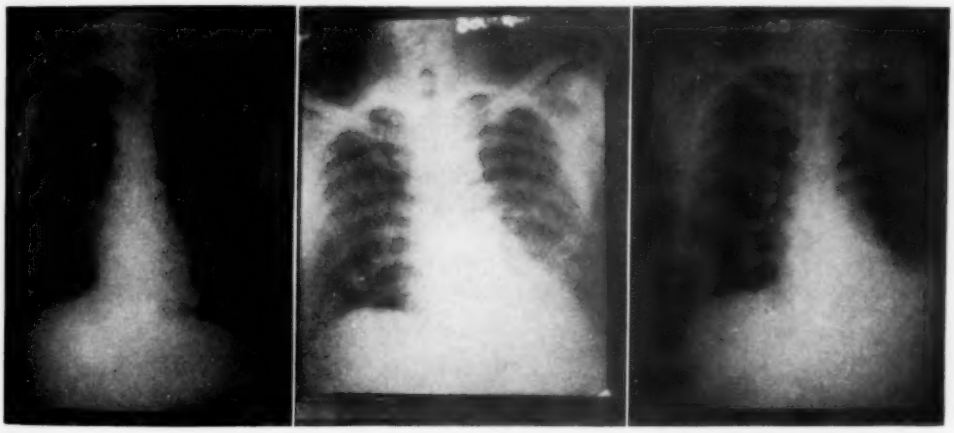
The importance also of the wound in the substance of the heart cannot be overlooked. There is an actual severance and necrosis of a localized portion of myocardium. In addition, the surrounding muscle is enveloped in suture material with resultant compression, trauma and ischemia of this larger area. Hesse,[4] in his article, cites two cases which died of pneumonia 6 and 18 days respectively after heart suture, in which autopsy showed the muscle about the wound to be necrotic, and two other cases in which aneurysm developed at the site of the operative scar. These are rare sequelae, but can be considered as indirect evidence of the destructive process which may occur in the sutured wound. In addition there is frequent ligation of a branch of the coronary vessels, usually the descending branch of the left coronary artery, either because it is damaged in the initial injury to the heart or because it is too close to the margin of the wound and has to be blocked by the sutures in order to close the hiatus in the myocardium. As a consequence of the closure of a coronary vessel, an infarct is probably always produced, in spite of the collateral circulation. Two cases of operative ligation of a coronary artery in human beings with postmortem demonstration of definite cardiac infarction have been found in the literature.[8, 9]

The electrocardiographic changes produced by pericarditis [10] consist of an early and transient elevation of the RT segment in the first two leads or in all three leads. This elevation is generally most marked in Lead II and has, therefore, aptly been called the T_2 type by Paul Wood.[11] The deviation is in the same direction (upward) in all leads, unlike myocardial infarction where it is opposite in direction in Leads I and III. Also no significant Q pattern is developed. The electrocardiographic picture of acute myocardial injury, on the other hand, depends upon the location of the lesion. Thus a lesion of the anterior left ventricular wall produces the characteristic T_1 type, with early upward deviation of the RT segment in Leads I and II and downward displacement of this segment in Lead III, followed by inversion of T_1 and T_2, whereas T_3 remains upright. No pattern due to anterior right ventricular injury in the human being has been definitely established, because infarction in this region almost never occurs.[12]

In our case report which follows and in the cases accumulated from the literature, an attempt has been made to evaluate the electrocardiographic tracings in terms of all the factors operative in influencing them—the postoperative acute inflammatory pericardial reaction, the localized injury to the myocardium generally in the anterior wall of either the right or left ventricle, and the cardiac infarction if a coronary vessel was ligated.

Case Report

The patient, C. B., was a 44 year old white male, who had had dementia praecox for five years and who had received a course of insulin shock therapy during the summer of 1938, with a great deal of improvement in his mental condition. At 9:15 a.m., September 3, 1939, he made a suicidal attempt by placing the point of a pencil of the eversharp type in the fifth intercostal space about 2 cm. medial to the nipple line, and throwing himself on his face, embedding the pencil in the chest wall. When seen by a physician shortly after, he presented the classical, much-described picture of cardiac tamponade, venous engorgement and cerebral anemia. At operation left hemopneumothorax was found, and a small transversely directed wound, about 4 to 5 mm. in diameter was observed on the obtuse margin of the base of the left ventricle, from which a thin stream of blood spurted with each systole of the heart. The wound was readily closed by a superficially placed purse-string suture. The postoperative course was uneventful, except for a moderate pericardial and slight left pleural effusion (figure 1). The air in the left side of the thorax was absorbed very rapidly. Electro-



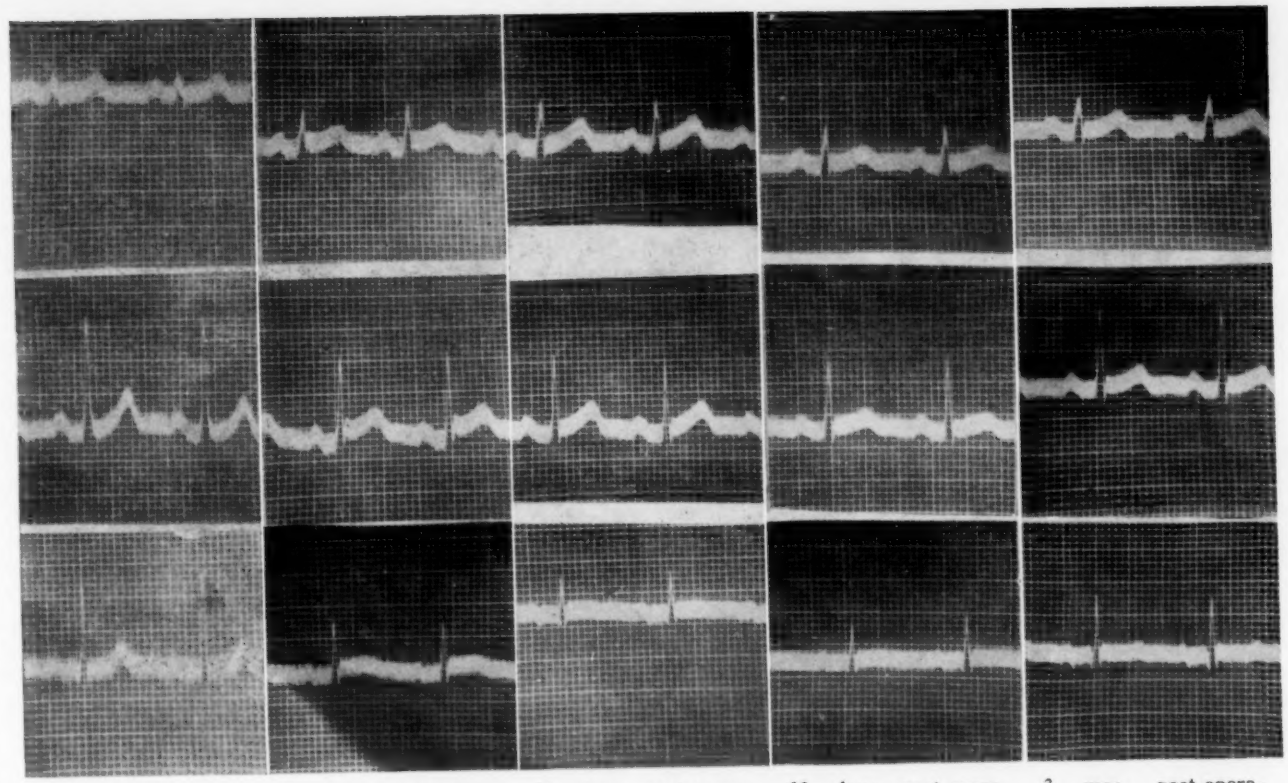
6 ft. plate, 1 mo. before operation.

Bed-side plate 4 days post-operatively, showing pericardial effusion.

Bed-side plate 20 days post-operatively, showing absorption of pericardial effusion, and presence of slight pleural effusion.

Fig. 1. Serial roentgenograms in Patient C. B.

cardiograms (figure 2) showed slight upward deviation of the RT segments in all leads, most marked in Lead II. These changes were apparent on the third postoperative day when the first tracing was taken and gradually diminished in extent until the tenth postoperative day, when the RT segments were again isoelectric except for the one in Lead II, which has continued to retain a barely perceptible elevation above the base line. At no time did the T-waves in any leads become inverted. Thus the electrocardiographic picture was that of the typical T_2 variety, presenting early transient changes most likely due to pericarditis. Other changes consisted of diminution in amplitude of the QRS complex in Leads II and III and flattening of the T-wave in Lead III.



15 mos. before operation.

3 days post-operatively. RT_1 elevated 1 mm.; RT_2 2 mm.; and RT_3 1 mm. QRS complex diminished in size in Leads II and III. P-wave diphasic in Lead III.

10 days post-operatively. RT segments return to isoelectric line. T_3 flattened.

23 days post-operatively. Some diminution in amplitude of T-waves in all leads. EKG taken 42 days p.o., essentially the same.

3 mos. post-operatively. EKG taken 4 mos. p.o., the same.

FIG. 2. Serial electrocardiograms in Patient C. B.

Results

The following table (table 1) contains a summary of the pertinent electrocardiographic findings in the 22 previously published cases, which are all that could be found in the medical literature available to us, and the present case report. Six of these had no early electrocardiograms, and three of the remainder had no late electrocardiograms because the patients died. A brief statement of the pathological findings of the heart in four patients is also made.

Discussion

In 15 of the 17 cases listed in the above chart, in which tracings during the first week were taken, a T_2 type of curve appeared. The RT segments were elevated in the first two leads or in all leads, and generally most markedly in Lead II. In case 18 this was rapidly followed by T-wave inversion in all leads as early as the third day, which by the sixth day was showing signs of becoming upright again. In some of the patients, such as numbers 11, 12 and 14, the RT elevation in Lead III was very slight and was followed by transient T-wave inversion in that lead, which had usually disappeared by the end of the first week. These curves occurred early and were transient, as occurs typically in pericarditis.

The tracings made from two weeks to one month after suture of the heart wound were characterized generally by bow-shaped RT segments starting from the isoelectric line and by inverted T-waves. These reverted to normal in from two to six months in most cases. In wounds of the anterior surface of the left ventricle, with or without involvement of branches of coronary arteries serving this region, a late T_1 type of curve with inversion of T-waves in Lead I or Leads I and II was found. In those patients with injury to the right anterior ventricular wall, without damage to coronary vessels supplying the left ventricle, T-wave inversion in all three leads was present. Case 19 of this group was complicated by purulent pericarditis, which may have produced sufficient inflammatory destruction of the superficial layers of the myocardium to cause the T-wave changes. The latter changes in that case would have no bearing on the location of the wound. The remainder of this group of cases, although small in number, suggests that an injury of the anterior wall of the right ventricle may in its later stages produce T-wave inversion in all leads. This does not mean that lesions in other localities or combined lesions may not produce a similar electrocardiographic picture. Crawford et al.,[28] in contrast to the above, have demonstrated that cauterization of the base of the anterior surface of the right ventricle in cats produced no electrocardiographic changes. According to the muscle bundle method of electrocardiographic localization of Robb and Robb,[29] however, an injury of the superficial sinospiral muscle, part of which composes the outer layer of the wall of the anterior surface of the right ventricle, produces elevation of the RT segments in all leads and subsequent in-

TABLE I

Case Reports with Electrocardiographic Findings

Case No.	Author, Year	Age, Color	Characteristics of Heart Wound	P.O. pericarditis	Initial RT Changes		Subsequent RT Changes		T-Wave Inversion		T-Wave Return to Normal		Q-Wave Changes If Any	Comments
					Time	Nature	Time	Nature	Time	Nature	Time	Final Picture		
1	Hyman and Fisher[13] 1926	24 negro	A.L.V., high up, not far from interventricular groove. Meas. 1½" ext. and 1" int.	Yes					1 EKG 9 mos. P.O.	T_1 −2 mm. T_2 and T_3 upright	1 EKG 1 yr. P.O.	T_1 diphasic +.5 −1 mm. T_2 and T_3 upright	Significant Q_1 in first tracing, became small in second	Late T_1 type
2	Bates and Talley[14] 1929	28 negro	A.L.V., near rt. boundary and upper border	Yes			1st EKG 5 days P.O.	RT_1 +5 mm. RT_2 +4 RT_3 iso-electric (T_3 inverted)	20 days P.O. 26 days P.O.	T_1 and T_2 inverted T_3 upright T inverted in all leads	3 and 8 mos. P.O.	T_1 and T_2 upright T_3 inverted	Small Q_3 and Q_3 seen in 12-day tracing and from then on	Early T_1 type; late T_1 type. T_3 however was inverted in all tracings except for transient period during acute inversion of T_1 and T_2 when it was upright
3	Elkin and Phillips[15] 1931— Case 2	25 negro	A.L.V., to left of desc. branch of lft. cor. (not ligated). Meas. 1.5 cm. externally	Yes					1st EKG 3 wks. P.O.	T inverted in all leads	6 mos. P.O.	T_1 upright T_2 diphasic T_3 inverted	Small Q_3 develops after 7 weeks	Late T_1 type. T_3 persistently inverted, after T_1 and T_2 have become upright
4	Holubec[16] 1935	12 white	Transversely into L.V. Meas. 8 mm. externally	?					1 EKG 37 days P.O.	T_1 inverted T_2 diphasic T_3 upright			Small Q_1	Late T_1 type. (Taken from P. Wood[11])
5	Kienle[17] 1938	25 white	A.L.V., near apex and parallel to rt. ventricle. Meas. 6 cm. externally	Yes	28 hrs. P.O.	RT_1 +.5 mm. RT_2 +1 RT_3 −.25	34 hrs. P.O.	RT_1 and RT_2 as before. RT_3 iso-electric						Initial T_1 type; subsequent T_2 type. Died 42 hours P.O. Autopsy showed fibrinous pericarditis
6	Present Case Report	44 white	Transversely into left ventricle, near base. Meas. .5 cm. externally	Yes			3 days P.O.	RT_1 +1 mm. RT_2 +2 RT_3 +1	23 and 42 days P.O.	T_1 and T_2 upright T_3 flattened	3 mos. P.O.	T-waves same as previous	None	Early T_2 type. No late signs of myocardial injury
7	VanderVeer and Norris[8] 1937	18 white	Laceration of rt. auricle, just above a.v. junction	Yes	1 EKG 15 hrs. P.O.	RT_1 +1 mm. RT_2 +2 RT_3 iso-electric								Died 36 hours P.O. Autopsy showed fibrino-purulent pericarditis

TABLE I (*Continued*)

Case No.	Author, Year	Age, Color	Characteristics of Heart Wound	P.O. pericarditis	Initial RT Changes		Subsequent RT Changes		T-Wave Inversion		T-Wave Return to Normal		Q-Wave Changes If Any	Comments
					Time	Nature	Time	Nature	Time	Nature	Time	Final Picture		
8	Porter and Bigger[18] 1932—Case 1	23 negro	A.L.V., on lft. border and parallel to long axis, and 5 cm. from apex. Meas. 1 cm. externally. Desc. branch lft. circumflex cor. ligated	Yes	14 hrs. P.O.	RT_1+2 mm. RT_2+2 $RT_3-1.5$	4 and 5 days P.O.	RT_1+2 mm. $RT_2+2.5$ $RT_3+.5$ (T_3 flat)	34 days P.O.	T_1 and T_3 inverted T_2 upright	63 days P.O.	Upright in all leads	Small Q present in all leads in all tracings. Largest in Lead III early, growing smaller with time	Initial T_1 type; subsequent T_2 type; late T_1 type
9	Davenport, Blumenthal and Cantril[19] 1935	32 negro	A.L.V., at apex, size of point of ice pick. Ant. desc. branch of lft. cor. artery and vein ligated	Yes	5 hrs. P.O.	RT_1+1 mm. RT_2+1 $RT_3-.25$ (T_3 invert.)	2 days P.O.	RT_1+2 mm. RT_2+1 RT_3-1 (T_3 upright)	2 wks. P.O.	T_1 inverted T_2 diphasic T_3 upright	6 mos. P.O.	Upright in all leads	Significant Q_3 appears 5 hrs. P.O., becomes smaller with time and R_3 precedes it	Early T_1 type; late T_1 type
10	Davenport[2] 1924	44 white	A.R.V., in upper portion of middle third. Meas. 5 mm. Interventricular branch of lft. cor. artery and vein ligated	?					19 days P.O.	Inverted in all leads	8½ mos. P.O.	Upright in all leads	Small Q_3 and Q_1 appear in 1st tracing; present throughout	Late inversion of T in all leads
11	Purks[22] 1931	18 negro	A.R.V., near interventricular septum. Desc. branch of lft. cor. artery ligated in its middle third	Yes	10 min. P.O.	RT_1+1 mm. RT_2 isoelectric RT_3-1	2 days P.O.	RT_1+3 mm. RT_2+3 $RT_3+.5$ (T_3 inverted)	16 days P.O.	T_1 inverted T_2 slightly inverted T_3 upright	2½ mos. P.O.	Upright in all leads	Small Q_2 and Q_3 present 2nd day. Diminished in size later but varying in size from time to time	Initial T_1 type; subsequent T_2 type; late T_1 type
12	Elkin and Phillips[15] 1931—Case 1	18 negro	A.R.V. Desc. branch of lft. cor. artery ligated	Yes	10 min. P.O.	RT_1+1 mm. RT_2 isoelectric RT_3-1	1½ days P.O.	RT_1+3 mm. RT_2+3 RT_3+1 (T_3 diphasic)	16 days P.O.	T_1 inverted T_2 and T_3 upright	3 mos. P.O.	Upright in all leads	Small Q_2 and Q_3 present throughout	Initial T_1 type; subsequent T_2 type; late T_1 type
13	Schlomka[8] 1931	21 white	A.R.V. Meas. 2 to 3 cm. long. Ant. desc. branch of lft. cor. artery ligated				1 EKG 7 days P.O.	Elevated in all leads, greatest in Lead II	21 days P.O.	T_1 and T_2 inverted T_3 small but upright			Significant Q_3 present at 7 days, absent at 14 days, present at 21 days	Early T_2 type; late T_1 type. Death in 4th week. Autopsy showed ant. left ventricular infarction and beginning aneurysm formation

TABLE I (*Continued*)

Case No.	Author, Year	Age, Color	Characteristics of Heart Wound	P.O. pericarditis	Initial RT Changes		Subsequent RT Changes		T-Wave Inversion		T-Wave Return to Normal		Q-Wave Changes If Any	Comments
					Time	Nature	Time	Nature	Time	Nature	Time	Final Picture		
14	L. Fischer[20] 1937	16 white	A.R.V. Meas. 2 fingers'-breadth. Ant. desc. branch of lft. cor. artery ligated	?			2 to 8 days P.O.	Elevated in all leads, greatest in Lead II	16 days P.O.	T_1 and T_2 inverted T_3 upright but small	4½ mos. P.O.	T_1 still inverted T_2 and T_3 upright	Small Q_1 and Q_3 persist throughout	Early T_2 type; late T_1 type
15	Angeli[21] 1938	24 white	A.R.V., near apex. Meas. 5 to 6 mm. Desc. branch of lft. cor. artery ligated	?					1 EKG 14 days P.O.	T_1 and T_2 inverted T_3 iso-electric	1 EKG 10 mos. P.O.	Upright in all leads	None	Late T_1 type
16	Porter and Bigger[18] 1932—Case 2	36 negro	A.R.V. About 5 cm. above apex. Meas. 1.5 cm. externally	?			9 hrs. to 9 days P.O.	RT_1+1 mm. RT_2+2 RT_3+1	33 days P.O.	Inverted in all leads	4½ mos. P.O.	T_1 iso-electric T_2 and T_3 upright	Small Q_2 and Q_3 present on 1st day; gone by night. Small Q_1 present on 33rd day; absent at 4½ months	Early T_2 type; late inversion of T in all leads
17	Ramsdell[23] 1934	41 negro	A.R.V.	?					1 EKG 5½ mos. P.O.	T_1 diphasic and slg. inv. T_2 and T_3 inverted			None	Late inversion of T in all leads
18	Davenport and Markle[24] 1934	22 negro	A.R.V., to rt. of interventricular groove. Meas. 1½" externally	Yes	12 hrs. P.O.	RT_1+2 mm. RT_2+4 RT_3+2	3 days P.O.	T_1 diphasic T_2 and T_3 inverted	6 days P.O.	T_1 upright T_2 diphasic T_3 slg. inverted	3 mos. P.O.	Upright in all leads	Small Q_3 present throughout	Early T_2 type. T-wave inversion on 3rd day; approaching normal on 6th. No late T-wave inversion indic. myocardial injury
19	Koucky and Milles[2] 1935	16 white	A.R.V., middle third, 1.5 cm. to rt. of and parallel to ant. desc. branch of lft. cor. Meas. 3 cm.				1 to 9 days P.O.	Elevated in all leads	25 days P.O.	Inverted in all leads	5 mos. P.O.	Upright in all leads	None	Early T_2 type; late inversion of T in all leads. P.O. purulent pericarditis
20	Warthen[25] 1935	15 negro	A.R.V., 1 cm. from lft. cor. and 2 cm. from base of pul. artery. Meas. 1.5 cm. externally	Yes			1 EKG 3 days P.O.	RT_1+.5 mm. RT_2+1 RT_3+.25	1 EKG 15 days P.O.	Beginning inversion of T_1 and T_2. T_3 inverted	1 EKG 4 mos. P.O.	Upright in all leads	None	Early T_2 type; late inversion of T in all leads

TABLE I (*Continued*)

Case No.	Author, Year	Age, Color	Characteristics of Heart Wound	P.O. pericarditis	Initial RT Changes		Subsequent RT Changes		T-Wave Inversion		T-Wave Return to Normal		Q-Wave Changes If Any	Comments
					Time	Nature	Time	Nature	Time	Nature	Time	Final Picture		
21	Gissane and Schulenberg[26] 1937	23 white	A.R.V., ¾" to right of interventricular groove. Meas. ¾". P.R.V., small wound	?			2 days P.O.	RT_1 and RT_2 elevated, greatest in Lead II RT_3 isoelectric (T_3 inverted)	21 days P.O.	Inverted in all leads	5 mos. P.O.	Upright in all leads	Rt. axis deviation throughout. Q_3 significant in first 2 tracings; small in 3rd	
22	Matti[3] 1938	24 white	A.L.V., at base and close to obtuse margin, small slit-shaped opening. P.L.V., at base of ventricle and near obtuse margin, small wound. Desc. branch of circumflex branch of lft. cor. artery ligated	Yes	1 day P.O.	RT_1 and RT_2 elevated, greater in Lead I RT_3 slightly depressed	2 days P.O. 4 days P.O.	RT_1 and RT_2 same RT_3 isoelectric RT segments as above (T_3 slightly negative)					Significant Q_{1} throughout	Died on 7th P.O. day. Autopsy showed fibrinous pericarditis. Infarct on the border of lft. ventricle between ant. and post. wall, meas. 5 cm. vertically and 3 cm. horiz.
23	Mondry[47] 1939	30 white	A.R.V. Meas. 3 cm. long A.L.V., near lft. margin. Meas. 3.5 cm. P.L.V., small, circular wound No arteries ligated				2 days P.O.	RT_1 and RT_2 elevated equally RT_3 isoelectric (T_3 isoelectric)	20 days P.O.	T_1 and T_2 inverted T_3 diphasic	6 mos. P.O.	Upright in all leads	None	

version of the T-waves. This appears to substantiate the interpretation here presented.

Those patients with wounds of the anterior right ventricular wall close to the interventricular septum with ligation of the descending branch of the left coronary artery showed a late T_1 type of tracing, probably because the bulk of the muscle in the infarct of the anterior left ventricular wall was much greater than that damaged in the injury of the right ventricle itself. There was one exception, case 10, which had inverted T-waves in all leads.

T-wave inversion in Leads I and II in anterior left ventricular injury, and inversion in all leads in right ventricular injury was also found by Paul Wood [11] in 1937, when he reviewed 13 cases of stab wounds of the heart and added one of his own. However, he attributed the picture in cases involving the left ventricle to myocardial injury and in cases involving the right ventricle to hemopericardium. Since hemopericardium occurs in injuries to either ventricle, it is difficult to see how it could be responsible for the electrocardiographic behavior in the case of one and not in the case of the other.

The conception here stated, therefore, is that the electrocardiographic alterations in the first week or 10 days following suture of a heart wound are due to pericardial inflammation which in most cases is of the serofibrinous variety. The T-wave inversion which is found two weeks to a month later, we believe, represents late evidence of destruction of a localized area of the myocardium by the original traumatizing agent, subsequent suturing and infarction if a coronary vessel was ligated. This view is in essential agreement with the conclusions of Barnes [30] regarding myocardial infarction complicated by pericarditis. He reported a number of cases, of which two came to autopsy, in which there was early RT elevation in all leads due to pericarditis. Localization of the infarct in the anterior or posterior wall of the left ventricle was only possible on the basis of a distinctive Q pattern or T-wave inversion of the T_1 or T_3 type.

Q-wave changes in the case reports here reviewed did not give any clue as to the location of the damaged muscle. In some of the tracings small Q-waves, and in a few instances significant Q-waves, appeared in one or more leads. They showed considerable variation in size from one electrocardiogram to the next, diminishing in size in some and increasing in size in others as time went on. These Q-waves were probably due to change in position of the heart, because of manipulation at operation and because of postoperative effusions and adhesions in the pericardium and pleura.

To refer back again to the RT segment changes in the first week, it might be asked what the picture would be if pericarditis were not present or did not produce electrocardiographic alterations, which it does not do in every case.[10] Where the anterior wall of the left ventricle is involved, elevation in Lead I and depression in Lead III of the RT segment would be expected. Such curves have been encountered early (from 10 minutes to 28 hours after operation) in four cases (5, 8, 11 and 12). They were evanescent and

rapidly superseded by RT elevation in all leads. In two additional cases (2 and 9) no clear-cut T_2 curve occurred at all, and the T_1 picture persisted throughout. Whether all injuries of this type would show a T_1 curve if the electrocardiograms were taken soon enough after operation is not known. In isolated anterior right ventricular injury no initial RT picture could be differentiated from that due to pericarditis, and it may be that the deviations are in the same direction as those due to pericarditis.

The three cases with multiple heart wounds also showed the T_2 type of curve early. The later findings represent a summation of electrical changes produced by the several areas of myocardial damage.

The case reported by us differs from all the others in that no T-wave inversion occurred at any time. Case 18 was similar in that the T-wave inversion was early and transient. In neither case was there electrocardiographic evidence of myocardial injury. The muscle lesions may not have been situated in the plane of the conventional leads, or they may have been too small to produce electrocardiographic changes.[31]

In order to verify or disprove these views on the electrocardiogram in penetrating wounds of the heart, many more case reports with early and repeated tracings will be necessary. It is also hoped that the location and extent of the injury to the heart will be carefully noted at operation and that postmortem studies of the existing pathological processes be made whenever possible in patients who do not survive.

Summary

1. Twenty-two cases of stab and gunshot wounds of the heart with electrocardiographic tracings have been collected from the literature, and another case report of a penetrating wound of the left ventricle is added.

2. The sutured wound of the heart wall is a localized area of myocardial injury, necrosis and cicatrization. Ligation of a coronary vessel, generally the descending branch of the left coronary artery, is a frequent complication. Serofibrinous pericarditis occurs in almost all cases postoperatively.

3. In injuries involving the anterior wall of the left ventricle or arteries supplying this region, electrocardiograms taken from several minutes to a number of hours after operation may show the T_1 type of picture with elevation of the RT segment in Lead I and depression in Lead III. These changes are generally superseded after the first day by electrocardiographic modifications due to pericarditis, but occasionally persist.

4. During the first week the electrocardiographic picture is that of pericarditis regardless of the location of the wound or whether a coronary artery is ligated. There is elevation of the RT segment in the first two leads or in all three leads, generally most marked in Lead II. This is called the T_2 type of tracing.

5. From two weeks to one month after operation, T-wave inversion is

fully developed, and may last from two to six months or more before reverting to normal. In anterior left ventricular injury, the inverted T-waves are in Lead I or Leads I and II. In anterior right ventricular injury, the T-waves are inverted in all leads. It is probable that these late T-wave changes are characteristic of localized myocardial necrosis and scar formation in these respective regions.

6. The present case report of a penetrating wound of the obtuse margin of the base of the left ventricle showed a T_2 type of picture during the first 10 days. No inversion of T-waves followed. The electrocardiographic picture was that of pericarditis. The myocardial lesion was " silent " either because it was small, or because it was not in the plane of the conventional leads. Similar electrocardiographic findings were present in Davenport and Markle's case, which, however, was a wound of the right ventricle.

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TACHYCARDIA AND SENSITIVITY TO HEAT AS INDICATIONS FOR BASAL METABOLIC RATE DETERMINATION *

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Since the principal function of the thyroid is to increase the oxidative processes in the body, patients with hyperthyroidism show an increase in their basal metabolism. Recognition of this fact by the medical profession has resulted in some abuse of a diagnostic procedure which should supplement and not replace clinical diagnosis. In recent years records in the Out-Patient Department of the Colorado General Hospital show that the number of basal metabolic rate determinations requested has mounted greatly without a corresponding increase in the percentage of abnormal tests. A study was undertaken, therefore, to determine if some physical sign or symptom of hyperthyroidism occurred with sufficient frequency to justify its use as a practical indication for the time consuming basal metabolic rate determination, or if the absence of some physical sign or symptom justified omitting a basal metabolic rate determination.

Table I

Year	Number of Basal Metabolic Rate Determinations	Number of Chemical Determinations on the Blood
1932	541	630
1933	605	795
1934	548	781
1935	350	636
1936	266	725
1937	360	921
1938	408	765

Although the study here presented was made upon a small group of patients, the conclusions have been utilized in the last four years on many hundreds of patients with such gratifying results that their presentation is considered of value. Mainly as a result of following closely the indications for basal metabolic rate determinations emphasized in this article, the number of needless basal metabolic rate determinations has been greatly reduced.† Table 1 shows the marked decrease in the number of basal metabolic rate determinations requested since 1934; the work to be reported was done in the early part of 1935. The figures for the number of chemical determinations on the blood requested during the same years are given for comparison.

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† Dr. Billings, Director of the Psychiatric Liaison Department, by increasing our knowledge of the psychoneuroses and thus improving our differential diagnosis of hyperthyroidism, has also helped decrease the number of needless basal metabolic rate determinations.

Methods

One hundred and forty-six patients from the Medical Out-Patient Department upon whom 150 consecutive basal metabolic rate determinations were performed constitute the material for this study. The patients were seen by many different physicians on the Staff. The physician recorded the lowest pulse rate obtained after the patient had been lying down for 10 minutes, the blood pressure, the size of the thyroid, the presence or absence of eye signs and tremor, subjective sensitivity of the patient to heat and cold, and changes in weight. Almost all the patients had had breakfast and had come some distance to the Clinic.

The patient, fasting since eight o'clock of the previous night, returned in one to several days for the basal metabolic rate determination. After the patients had rested for one hour in bed, the determinations were done in duplicate with a McKesson Metabolator. The pulse rate was counted several times during the determination and the *lowest pulse rate obtained and not the average pulse rate* was used in this work. Bierring standards were used for the boys from 13 to 18½ years, Boothby and Sandiford standards for girls from 13 to 18½ years, and Aub and Dubois standards for men and women over the above ages.

The subsequent clinical course of the patients was followed until a definite diagnosis was established, in the course of which many of the patients had repeated basal metabolic rate determinations.

Results

Since examination of the data at once revealed the importance of pulse rate and sensitivity to cold, the cases were analyzed solely on the basis of these two factors. A marked correlation between the basal pulse rate and the basal metabolic rate has been found by many workers. We were, however, more interested in determining the lowest pulse rate level associated with elevated basal metabolic rates or, more exactly, with hyperthyroidism. Since the initial diagnosis of hyperthyroidism must be made in the outpatient clinic or office, we were especially interested in the pulse rate as determined in the clinic. Clinic pulse rates are influenced by several factors in addition to those acting on basal pulse rates and therefore have not been used previously for correlation with basal metabolic rates. As a result of the influence of exercise, food, and excitement, the clinic pulse rates may be expected to be higher than the basal pulse rates and to show greater variation. Since only the lower level of pulse rates associated with abnormally elevated basal metabolic rates was desired, it was felt worthwhile to use the clinic pulse rates in the hope that the smallest increment produced by exercise, food, and excitement would be fairly constant. A comparison of the clinic and basal pulse rates for all cases is shown in table 2. Since only 28 of the patients were men, no attempt was made to separate the sexes, and the figures are essentially those to be expected in women. It is interesting to

note that only after the pulse rate in the clinic exceeds 95 does the basal pulse rate show an increase over what may be considered a normal level of 70 to 75.

Examination of the data revealed that basal metabolic rates over plus 15 were present in only two patients with basal pulse rates under 81. One of these patients, a 59 year old woman who complained of nervousness and poor appetite, had a basal metabolic rate of plus 24. Another basal metabolic rate done before the patient had received any treatment and at a time when the patient said she was feeling worse, was plus 1. The other patient, whose basal metabolic rate was plus 16, had asthma and had been diagnosed as being psychoneurotic. Other basal metabolic rates obtained on this patient were plus 5 and plus 14. Since neither of these patients was thyrotoxic the conclusion may be drawn that in this series no patient with hyperthyroidism had a basal pulse rate under 81.

TABLE II

Relation of Pulse Rate in Clinic to Pulse Rate During Basal Metabolic Rate Determination

Number of Cases	3	0	10	10	10	23	20	18	13	5	20	3	3	1	7	4
Pulse Rate in Clinic	46 to 50	51 to 55	56 to 60	61 to 65	66 to 70	71 to 75	76 to 80	81 to 85	86 to 90	91 to 95	96 to 100	101 to 105	106 to 110	111 to 115	116 to 120	Over 120
Average Pulse Rate during BMR	55	0	60	60	69	69	71	72	76	74	84	82	94	86	94	112
												88		93		

Basal metabolic rates over plus 15 were present in only four patients with clinic pulse rates under 96. Two of these four were the two patients described above. The other two were definitely thyrotoxic. One of these had a basal metabolic rate of plus 34 and a clinic pulse rate of 90. The clinic pulse rate on two other occasions was 104 and 96. The other patient was receiving Lugol's solution and showed a marked variation in her condition. Her pulse in the clinic at a time when she felt very well was 69; two days later her basal metabolic rate was plus 53 and her basal pulse rate 83. On her return to the clinic her pulse rate was 96 and it was evident that she had had a relapse since her previous visit. In this group of patients then, a clinic pulse rate of 96 appeared to be a good lower level for the pulse rate of patients with hyperthyroidism.

On examining the histories of all patients with pulse rates over 95 in the clinic, it was found that the patients could be divided into the following three groups: (1) a group with basal metabolic rates over plus 15 (table 3); (2) a group in which the basal metabolic rate was normal and in which organic disease of some nature—tuberculosis, other infections, cardiac disease—was present to account for the increased pulse rate; (3) another group composed of patients in whom the basal metabolic rates were normal but who had no organic disease to explain the symptoms which were in some

ways suggestive of hyperthyroidism (table 4). The surprisingly large number of patients in Group 3 (table 4) in whom the diagnosis of psychoneurosis was made and the preponderance of women are points worthy of emphasis. Because these patients have many symptoms suggestive of hyperthyroidism, they must be distinguished from the patients in Group 1 (table 3). The clinic pulse rates were high in both groups, but a definite

TABLE III

Cases with Clinic Pulse Rates Over 95 and Basal Metabolic Rates Over +15

BMR	Clinic P.R.	BMR P.R.	HIC*	Age	Sex	Remarks
+84	148	144	C	36	M	Definite clinical hyperthyroidism
+64	140	116	I–C	49	F	Definite clinical hyperthyroidism
+57	118	116	C	46	F	Definite clinical hyperthyroidism
+57	108	96	C	40	M	Definite clinical hyperthyroidism
+48	110	120	C	43	F	Definite clinical hyperthyroidism
+36	120	84	C	42	F	Hypertension. Chronic nephritis. Psychiatric diagnosis of schizophrenia. Gaining weight. Probably a polyglandular dyscrasia
+21	120	84				
+34	96	86	C	21	M	Myeloid leukemia
+31	96	120	C	57	F	Adenoma of thyroid with symptoms of hyperthyroidism. Hypertension and some signs of decompensation
+28	100	92	C	16	F	Definite clinical hyperthyroidism
+22	100	88	C	38	M	Definite clinical hyperthyroidism
+19	112	86	C	58	F	Diabetes mellitus with some symptoms of hyperthyroidism
+18	100	82		23	F	Bronchial asthma. Slight fever at time BMR was taken. Repeat BMR two months later −3
+17	120	96	H	54	M	C.N.S. lues. Heart enlarged. Aortic systolic murmur

* H = Patient prefers heat.
C = Patient prefers cold.
I = Patient is indifferent to heat and cold.

tendency for higher pulse rates existed among those with increased basal metabolic rates. During the basal metabolic rate determination the pulse rate fell in both groups. In the group with elevated basal metabolic rates the pulse rate fell from an average of 113 in the clinic to 101 during the basal metabolic rate determination. In no case did the basal pulse rate fall below 81. In the group with normal basal metabolic rates the pulse fell from 103 to 82. In this latter group many basal pulse rates were below 81, but it is important to note that probably as a result of excitement the basal pulse remained quite high in many patients.

It is evident that in the group of patients in whom the differentiation from hyperthyroidism is important the pulse rate may frequently be misleading. This is especially true of the pulse rate in the clinic but also true to a less extent of the basal pulse rate. Comparison of tables 3 and 4, however, shows a marked difference in the subjective sensitivity to heat of these two groups. In every case where the basal metabolic rate was elevated a definite preference for cold existed; whereas the group with normal basal metabolic rates either had no preference or definitely preferred heat.

TABLE IV

Cases with Clinic Pulse Rates Over 95 and Basal Metabolic Rates of +15 or Under
Organic pathology not sufficient to account for increased pulse

BMR	Clinic P.R.	BMR P.R.	HIC	Age	Sex	Remarks
+10	100	86	I	23	F	*Psychoneurosis*—tension state with anxiety attacks. Markedly labile pulse. Psychiatric consultation with improvement
+ 8	100	94				
+ 7	100	80	I–C	40	F	Depression with some anxiety features. Psychiatric consultation with improvement
+ 5	116	92	I–H	54	F	Nervousness and insomnia. Impressions: Hypertension. *Psychoneurosis*
+ 3	105	82	I	35	F	Anxiety state with tension. *Psychiatric consultation*
+ 3	104	68	H	32	F	Colloid goiter. Nervousness. Impression: *Psychoneurosis*
+ 1	120	106	I	42	F	Marked nervousness and tension. No organic pathology determined
+ 1	100	104	I–C	36	F	Complaint of nervousness. Impressions: Non-toxic adenoma of the thyroid. *Psychoneurosis*—Improvement with psychotherapy
− 5	100	84	H	38	F	Pain in left side. Menopausal symptoms
− 5	108	66	C	18	F	No definite diagnosis. Continuation of pain in right lower quadrant following appendectomy with no objective findings
− 6	96	68	H	44	F	Substernal feeling of pressure, palpitation, vague pains, "sick headaches." No objective heart findings
− 7	96	88	I	29	M	Nervousness and palpitation. *Psychoneurosis*—Improvement with psychotherapy
−10	100	72	I	31	M	*Psychoneurosis.* Psychiatric consultation
−12	100	75	I	31	F	Colloid goiter. "Thyroid choking her." Impression—*Psychoneurosis*
−15	96	62	H	18	F	Tired, dysmenorrhea. Taking thyroid gr. 1 daily at time of BMR

In summary it may be noted that in all but two cases, and even these two cases were not complete exceptions, every patient with hyperthyroidism

had a clinic pulse rate over 95 and was sensitive to heat. These two facts served to separate the hyperthyroid patients from the great majority of patients in whom hyperthyroidism was suspected but not present.

Discussion

The changes in the circulatory system in hyperthyroidism have usually been considered compensatory. The extra oxygen required by the cells is carried to the tissues by an increase in the total blood flow. Since the total blood flow varies with the heart rate and the output of each cardiac contraction, attempts have been made by Read,[1] Gale and Gale,[2] Jenkins[3] and Read and Barnett[4] to find formulae for the prediction of basal metabolic rate from pulse rate and pulse pressure. Opinion as to the value of these formulae has varied, but the general opinion was expressed by Comroe[5] when he stated that "the basal metabolic rate cannot be predicted from pulse rate and pulse pressure with sufficient accuracy and consistency to render the method a substitute for measurement by indirect calorimetry."

Since the total blood flow can be increased by merely increasing the output of each cardiac contraction, it would appear possible to have mild hyperthyroidism without elevation in heart rate. Increase in heart rate, however, according to recent work, may have another origin. The isolated perfused hearts of rabbits which have received thyroxin before death have been shown to continue to beat at an accelerated rate.[6] This increase in the rate of pulsation was shown by Markowitz and Yater[7] to be present in tissue cultures of fragments of heart muscle removed from chick embryos before the appearance of nerve elements in the heart. On the basis of these findings Yater[8] says that "it appears that the increase in the rate of circulation is a fortuitous rather than a physiological adjustment. It is due mainly to the increase in thyroxin in the myocardium which causes the heart to beat more rapidly and vigorously."

The rapid pulse takes on renewed significance: the heart rate in hyperthyroidism should always be greater than normal. The only true exception to an increased heart rate in hyperthyroidism occurs when the heart for some reason is refractory to the action of thyroxin. Since other tissues of the body are sometimes apparently refractory to thyroxin, this occurrence is possible but certainly cannot be common. An increased heart rate may apparently be absent when the normal rate is so low that the increase resulting from hyperthyroidism is not evident. Sturgis and Tompkins[9] followed a few patients with hyperthyroidism and apparently normal pulse rates and found that after thyroidectomy the pulse rates decreased to very low normals. The pulse rate, like the basal metabolic rate, may be normal during periods of spontaneous remission or during remission produced by iodine. In the presence of auricular fibrillation the pulse rate cannot be evaluated and the presence of this complication should not be overlooked.

The results given above indicate that the basal pulse rate in patients

with hyperthyroidism is usually above 80. The pulse rate will be higher in the clinic because of the effect of exercise, food, and excitement. Exercise produces an excessive increase in oxygen consumption and heat production in patients with hyperthyroidism [10] and might, therefore, be expected to increase the pulse excessively. The specific dynamic action of food in hyperthyroidism has been found to be normal by some investigators, increased by others.[11, 12] Because of an increased sensitivity to adrenalin and from the nature of their disease thyrotoxic patients might be expected to react excessively to excitement.[12] The three factors of exercise, food, and excitement appear therefore to operate to increase the basal pulse of the thyrotoxic patient to a greater extent than that of the normal person. From the data collected it appears that the increase in the basal pulse rate as a result of these factors is at least 15; so that 96 serves as a good lower limit for the pulse rate of thyrotoxic patients in the clinic.

Because their symptoms resemble those produced by hyperthyroidism, the patients with normal basal metabolic rates and with no evident organic disease to account for their symptoms are often incorrectly thought to be thyrotoxic. When the cardiovascular complaints are conspicuous the diagnosis of "effort syndrome," "irritable heart," or "neurocirculatory asthenia" is often made. Billings [13] found that almost half of these patients, whom he labels as having an "anxiety syndrome,"* were for varying periods of time incorrectly diagnosed and unsuccessfully treated for hyperthyroidism. Although a careful history, especially from a psychiatric standpoint, and a complete physical examination will usually establish the diagnosis, many can be separated from thyrotoxic patients merely by the presence of a pulse rate which is below 96 in the clinic and below 81 under basal conditions. Some of these patients, however, have rapid pulse rates under clinic conditions and, at times, even under supposedly basal conditions. Since the rapid heart rate is usually the result of a temporary decrease in vagal tone produced by psychic stimuli, diversion of the patient's attention results in an increase in vagal tone with slowing of the heart. A marked variation in the heart rate is therefore of value in recognizing these patients.

When the pulse rate fails as a guide, a difference in heat tolerance easily separates patients with anxiety syndromes from patients with hyperthyroidism. The thyrotoxic patient uses more oxygen and produces more heat. Under basal conditions this increase in heat production frequently amounts to 40 per cent of normal. This is approximately the heat produced by a normally active person. The thyrotoxic patient, however, not only starts from this elevated basal condition but shows an abnormal increase in his heat production in carrying out ordinary activity.[10] His heat production is continuously that of a person doing moderately heavy or even very heavy manual labor. This is essentially true even in mild cases. All this heat must be dissipated, the greatest portion by radiation, convection and con-

* The anxiety syndrome is one of the psychoneurotic reactions.

duction. Since the body loses heat more easily at lower environmental temperatures, these patients prefer cooler rooms and fewer clothes than normal persons. To help dissipate the heat, the capillaries in the skin are dilated and the blood flow through them is greatly increased in quantity and velocity. Loss of heat through evaporation from the skin is increased.

Since the surface area of the extremities constitutes 65 per cent of the body surface, heat dissipation from the extremities is correspondingly important. Maddock and Coller [14] found that the shift of blood to the surface of the body which results from an increase in body heat production is not uniform in all parts of the skin but is of much greater degree in the extremities than in the head and trunk. The increase in skin temperature is, accordingly, greatest in the extremities. They also found that the skin temperature of the great toes varied directly with the basal metabolic rate. These findings explain why the hands and feet of the patient with hyperthyroidism feel warm both to the patient and to the examiner.

Compare this condition with that which exists in the tense or anxious patient whose complaints and rapid pulse frequently make the differentiation from hyperthyroidism difficult. Heat production and total cardiac output are normal. The tension state frequently results in a spasticity of the vessels of the extremities, so that the blood supply is diminished and the blood flow sluggish. Characteristically, these tense, anxious patients have cold hands and feet.

In eliciting subjective sensitivity to heat, the question, "Do you like heat or cold better?" is as likely to receive a false as a true answer. Sensitivity to heat or cold is more accurately discovered by questions such as the following: "Do you like the house warmer or colder than the people around you?" "Do you use more or less bed covers than your husband?" "Are your hands and feet cold or warm?" "Do you now use less clothes in cold weather than previously?" A recent change in sensitivity is very important.

In emphasizing the importance of tachycardia and sensitivity to heat, it is not intended to minimize in any way the importance of other symptoms and findings and a careful evaluation of all the information which can be obtained. The practical value, however, of tachycardia and especially of sensitivity to heat for distinguishing the psychoneurotic from the thyrotoxic patients has been overlooked.

Summary

One hundred and forty-six patients have been studied from the standpoint of clinical diagnosis, pulse rate in the clinic, basal metabolic rate, pulse rate during the basal metabolic rate determination, and sensitivity to heat. The following observations are made:

The average basal pulse rate was not increased above the normal 70 to 75 level until the pulse rates in the clinic exceeded 95.

Hyperthyroidism was uncommon with a pulse rate in the clinic under 96 and a basal pulse rate under 81.

Patients with increased basal metabolic rates showed a definite tolerance to cold and sensitivity to heat which was important in distinguishing them from the psychoneurotics with whom they are most apt to be confused. The latter show either an indifference to heat or cold or a preference for heat.

Conclusions

1. If the pulse rate of a patient in the clinic is below 96, the patient probably does not have thyrotoxicosis.

2. If the pulse rate of a patient in the clinic is below 81, the patient almost certainly does not have thyrotoxicosis and a basal metabolic rate determination is therefore unnecessary.

3. If the patient expresses an indifference to heat and cold, thyrotoxicosis is probably not present.

4. If the patient prefers heat or complains of cold hands and cold feet, thyrotoxicosis is almost certainly not present and a basal metabolic rate determination is unnecessary.

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CLINICAL STUDIES WITH THE AID OF RADIO-PHOSPHORUS. IV. THE RETENTION IN BLOOD, THE EXCRETION AND THE THERAPEUTIC EFFECT OF RADIO-PHOSPHORUS ON PATIENTS WITH LEUKEMIA *

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Previous studies [19, 20, 21, 22, 34, 35] have shown that radiophosphorus ($_{15}P^{32}$) (which owes its radioactivity to the spontaneous emission of beta rays) when administered in the form of sodium phosphate, at first concentrates in the bone marrow and those tissues infiltrated with leukemic cells and later concentrates in the osseous tissues. Radio-phosphorus has been used as a therapeutic agent during the past three years in all types of leukemia, with encouraging results. The principal advantages offered by radio-phosphorus appear to lie in its ease of administration (it may be given orally, intravenously, etc.), in its therapeutic effectiveness and in the fact that nausea, "radiation sickness" and other symptoms do not occur following its administration. This report deals with the rate at which P^{32} is absorbed into the blood and is excreted in the urine and feces of various patients and normal individuals, in addition to its therapeutic effectiveness in patients with leukemia. One hundred case studies are presented.

Materials and Methods

A. Radio-phosphorus.

1. Production and quantitation.

The radioactive phosphorus was produced by the Berkeley cyclotron.[18] This instrument directs streams of very rapidly moving (16 Mev) deuterons (nuclei of heavy hydrogen) into ordinary red phosphorus (atomic weight, 31), and thereby converts some of it into radioactive phosphorus (atomic weight 32), which emits beta-particles only, with energies averaging 600,000 electron-volts and has a half-life of 14.3 days (i.e., at the end of a period of 14.3 days, one-half as many beta-rays are emitted as were being emitted at the start of the period). During bombardment the number of phosphorus atoms that become radioactive depends on the number and the energies of the striking deuterons. At present about one in every million atoms is made radioactive. This mixture of radio-phosphorus and inactive phosphorus is then converted into an aqueous solution of dibasic sodium phosphate

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(Na_2HPO_4) of various concentrations (15 to 50 mg. per c.c.) for oral and intravenous use. The amount of radiation emitted by the sodium phosphate solution depends upon the number of atoms of radioactive phosphorus present. When a sample emits 3.7×10^7 beta-particles per second it is said to contain one millicurie of beta-radiation. One microcurie is 1/1000 of a millicurie. Because of the innumerable factors which must be taken into consideration it is difficult to discuss this type of radiation in terms of "r" units with which the roentgenologist is familiar, but the radiations emitted by radio-phosphorus may be converted into "r" units by using the following equivalents: 1 microcurie = 37,000 beta-particles per second; 1 "r" = 1 e.s.u. of ions per cubic centimeter of air at S.T.P. The number of beta-particles multiplied by their average energy gives the total energy. This total energy, divided by the energy required to form one ion pair (about 32 eV) gives the number of ion pairs. Therefore the number of ion pairs formed by one microcurie of radio-phosphorus per second is equal to 37,000 (number of beta-particles) $\times$ 600,000 (average energy of one beta-particle) divided by 32 (energy to form one ion pair) $= 7 \times 10^8$. To compare this with 1 "r" unit in water (or tissue) we must consider that 1 "r" unit in air = 1 e.s.u./c.c. $= 2.1 \times 10^9$ ion pairs/c.c.; the same dose of x-radiation in water produces an ionization greater than this by the ratio (density of water) divided by (density of air), or $2.1 \times 10^9 \times 800 = 1.7 \times 10^{12}$ ion pairs/c.c. Therefore 1 microcurie of radio-phosphorus contained in 1 c.c. of water produces an ionization in this volume equal to 7×10^8 divided by $1.7 \times 10^{12} = 4.1 \times 10^{-4}$ "r" units per second. The dose in one day is now obtained by multiplying this result by the number of seconds in a day (86,000), which gives the result:

> 1 microcurie/c.c. of water physically equals approximately 35 "r" units, dosage per day.

Thus, according to the above calculations, if a man weighing 50 kg. completely absorbed 1 millicurie of radio-phosphorus, and if these atoms are temporarily and evenly distributed throughout the body, he would be receiving in terms of roentgens the following calculated dose of irradiation for twenty-four hours:

> 1 μ c/50 gm. (body weight) = 1/50 μ c/gm. or c.c. of tissue.
> $1/50 \times 35 = 35/50$ or 0.7 "r" whole body irradiation in 24 hours.

Since absorption is not complete, and since there is excretion and decay of P^{32}, the actual dose of irradiation decreases from day to day. Furthermore, the phosphorus atoms are not uniformly distributed and some tissues, such as bone marrow and tissues infiltrated with leukemia cells, receive by far the greatest amounts of irradiation.

The words "microcurie" or "millicurie" which appear throughout this paper refer to the number of beta-particles per second emitted by the solution

or tissue in question, as compared with a uranium standard (which emits 500 beta-particles per second), and not to standards emitting mixed radiations (alpha, gamma and beta) such as radium.

2. Dosage.

After the solution of dibasic sodium phosphate has been assayed for radioactivity, it may be administered by several routes. The most convenient is, of course, the oral route. The solution is mixed with equal parts of orange juice and is administered to the patient before breakfast.[8] It may be given intravenously, intraperitoneally, subcutaneously, intramuscularly, directly into tumors, or as an unction.

Single oral doses have varied from 1 to 20 millicuries, depending on the age of the patient and the type of the disease; single intravenous doses have varied from 0.5 to 6 millicuries. Less than 3 grams of sodium phosphate have been administered orally in each dose; less than 1 gram when given intravenously. Two factors especially have governed the dosages administered to the patients reported in this paper. First, tolerance of patients to irradiation of any kind varies markedly so that the first doses given were always small. Second, the concentration of radiation had to be kept at a level which would do only minimal damage to the normal cells of the body. The first doses administered were determined by the following considerations:

a. The lethal dose of radio-phosphorus for a 20-gram mouse is approximately that amount given intraperitoneally which emits 70 microcuries of beta-radiation; for a 6-pound monkey, 7 millicuries by the same route. These results suggest that the lethal dose of radio-phosphorus for an average adult human would be well over one hundred millicuries.

b. By the Heublein technic[4] as much as 20 " r " of x-radiation have been administered to the whole body daily for a period of three weeks' time to patients with various diseases.

Therefore the first doses of radio-phosphorus administered to adult patients were those which emitted between 1 and 5 millicuries of beta-radiation. The succeeding doses varied according to the clinical status and the levels of the red and white blood cells of the patient—the same guides used by roentgenologists.

Since the half-life of radio-phosphorus is but 14.3 days, there is no danger of cumulative radiation effects similar to those produced by such agents as radium or thorium which have half-lives of hundreds of years. Furthermore, from 25 to 50 per cent of a dose of radio-phosphorus is excreted by normal individuals during the six days after administration and 1 to 2 per cent daily thereafter. At that rate of excretion and considering the constant rate of decay, about 15 per cent of a dose would be retained at the end of two weeks. Six to eight weeks after a single administration of radio-phosphorus only insignificant amounts of radiation are found in any tissue, including the osseous tissues.[5]

Clinical Data Previous to Administration of Radio-Phosphorus

					Phy. and Lab. Findings on Adm.						Biopsy		
Name and Numbers	Sex and Age	Date of Admission	Chief Complaints and Duration of Chief Complaints on Admission	Diagnosis and Treatment Previous to Admission	Characteristics of Peripheral Lymph. Nodes	Extension of Spleen Below Costal Margin in Cm.	Extension of Liver Below Costal Margin in Cm.	Other Findings	On Admission: Hb (%) Sahli	On Admission: WBC/Cu. mm. in 1000's	M = Sternal Marrow L = Lymph Node R = Rib Marrow S = Skin Hyper = Hyperplastic	Chemistry and Serology, etc.	Roentgenological Findings R = Rarefaction
1	2	3	4	5	6	7	8	9	10	11	12	13	14
TABLE I													
1 Mie	M 43	5/27/40	Fracture external malleolus of right foot		Normal	None	None	Body weight 201 lbs.	77	6		Wass.-neg.	
2 Per	M 35	7/19/40	Fracture external malleolus of right foot		"	"	"	Body weight 154 lbs.	85	8		Wass.-neg.	
3 Rob	M 31	3/25/40	Fracture radius of right arm		"	"	"	Body weight 144 lbs.	93	7			
4 Vic	M 32	6/17/40	Wire (4.5 cm.) foreign body removed surgically from right foot		"	"	"	Body weight 152 lbs.	85	6		Wass.-neg.	
TABLE IV													
92 Agn	M 40	2/ 9/38	Fatigue, Anorexia, Cough } 5 mo.; Abdominal pain—3 wks.	None No R	Small and shotty	1		Fundal hemorrhage and pallor	75	41	S. lesion—no leukemia infiltration M—hyper (many monoblasts)	Wass.-neg.	
* 93 Mac													
TABLE V													
a. Lymphemic													
94 Bio	M 59	5/19/39	Generalized aches, Weakness } 2 wks.	None No R	Small and shotty	2	4		70	10	M—hyper infiltrated with plasma cell R—plasma cell infiltration	Total blood protein 6.6% Bence-Jones Proteinuria ++++	
b. Non-Lymphemic													
95 Ril	M 42	6/ 7/40	Backache—1 yr.	Multiple myeloma March 1940 X-radiation—amount unknown	Shotty				77	4	M—hyper 15% plasma cells	Bence-Jones Proteinuria +++	Diffuse R bony destruction of many bones

* Previously published.

Pat.	Treatment: Radiation	Treatment: Transfusion			Clinical Data after Administration of Radio-Phosphorus: Phy. and Lab. Findings			Remissions			Postmortem Findings			Pat. Studies	
Dates and Total Dosages of Radio-Phosphorus (in Millicuries) Adm. O = Orally I.V. = Intravenously	X-Radiation or Neutron Radiation and Dates	Dates	Number	Total Amount of Blood in c.c.	LN = Lymph Node S = Spleen L = Liver - - - - - - - - - - I = Increased D = Decreased U = Unchanged } Refers to } Change in Size	Min. and Max. Levels: Hb (%) Sahli	Min. and Max. Levels: WBC/Cu. mm. in 1000's	Clinically and Hematologically Normal for a Period of 1 Year	General Condition of Patient on Mar. 15, 1941	Date of Death	Hours Between Death and Autopsy	Gross Findings (Weight in Grams)	Microscopical Findings	Peripheral Blood = PB Excretions = E Tissue = T	Number
15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Normal Persons															
7/22/40 1.5 (O.)						76 to 77	6 to 7							P B E	1
7/22/40 1.5 (I.V.)						76 to 85	5 to 8							P B E	2
7/22/40 1.5 (O.)						88 to 93	7 to 8							P B E	3
7/22/40 1.5 (I.V.)						84 to 85	6 to 7							P B E	4
Monocytoid Leukemia (Acute)															
2/1/39 to 3/3/39 6.9 (O.)										3/ 6/39	4	Gums swollen and ecchymotic Liver 2840; spleen 900 Bone marrow —red	Reticulo-endothelial hyperplasia of most organs including the kidneys and submucosa of G.I. tract	T	92
1/13/38 to 2/18/38 23.24 (O.)										2/21/38	18	Gums edematous and ecchymotic Liver 2325; spleen 750 Marrow—red	Monocytoid infiltration lungs and heart, kidneys, adrenal, ovaries, breast, submucosa of G.I. tract, gall bladder, liver and hemopoietic organs	T	93
Plasmacytoid Leukemia (Acute)															
a. Lymphemic															
6/10/39 to 6/29/39 14.9 (O.)		6/10/39 to 6/25/39	6	3000	LN—U S—U L—U	30 to 70	10 to 20			8/19/39	17	Liver 2720; spleen 760 Marrow—red	Plasma cell infiltration of most organs including marrow, kidneys and submucosa of G.I. tract	T	94
b. Non-Lymphemic															
6/7/40 to 9/3/40 20 (O.) 12/8/40 to 2/12/41 4.6 radiostrontium		11/7/40 to 3/1/41	2	1200	LN—U S—U L—U	50 to 77	1 to 4	Good (Pt. being treated with radiostrontium)						P B E	95

Clinical Data Previous to Administration of Radio-Phosphorus

Name and Numbers	Sex and Age	Date of Admission	Chief Complaints and Duration of Chief Complaints on Admission	Diagnosis and Treatment Previous to Admission	Characteristics of Peripheral Lymph Nodes	Extension of Spleen Below Costal Margin in Cm.	Extension of Liver Below Costal Margin in Cm.	Other Findings	Phys. and Lab. Findings on Adm. On Admission: Hb (%) Sahli	Phys. and Lab. Findings on Adm. On Admission: WBC/Cu. mm. in 1000's	Biopsy: M = Sternal Marrow, L = Lymph Node, R = Rib Marrow, S = Skin, Hyper = Hyperplastic	Chemistry and Serology, etc.	Roentgenological Findings R = Rarefaction
1	2	3	4	5	6	7	8	9	10	11	12	13	14

TABLE VI.

a. Myeloid (Associated with Neuroblastoma)

96 Rich	M 10 mo.	4/ 7/39	Mass in upper right quadrant and in left supraclavicular region—3 mos.	None No R	Left supra-clavicular 3 cm. in diam.		7		85	13	L—neuro-blastoma	NPN—49.5 Ca.—9.7 Phos.—5.8 } mg./100 c.c.	R—most bones

b. Myeloid (Associated with Polycythemia)

97 Hey	M 59	2/14/40	Weakness Mass in abdomen } 24 yrs. Loss of weight (50 lbs.) during previous 6 mos.	Leukemia March 1938 X-radiation	Shotty	24	6		110	55	M—hyper normal differential with 30% normoblasts	Sedimentation 1 mm./hr. Wass.—neg.	

c. Lymphoid (Associated with Leukosarcoma)

98 Mil	M 52	1/ 9/41	Generalized lymphadenopathy Ascites Edema of lower extremities	Leukosarcoma with leukemia Dec. 1940 No R	Gen. enlarg. 3×	1	1	Scrotal edema	81	45	L—Lymphosarcoma		

d. Monocytoid (Associated with (99) Chloroma and (100) Diffuse Miliary Tuberculosis)

99 Ave	M 11	1/ 2/41	Weakness and enlargement of the cervical nodes Nov. 1940	Lymphosarcoma Nov. 1940 Much X-radiation	Gen. enlarg. 3×	2	1	Protrusion of eyes and generalized subcutaneous masses	86	3	L—leukemic infiltration		
100 Bla	F 32	4/ 6/39	Weakness Headache } 4 wks. Fever	None No R		1			59	12		Wass. and heterophile antibody—neg.	

I, IV, V AND VI (*Continued*)

Treatment						Clinical Data after Administration of Radio-Phosphorus										
Rx	Radiation		Transfusion			Phy. and Lab. Findings			Remissions				Postmortem Findings		Rx Studies	
Dates and Total Dosages of Radio-Phosphorus (in Millicuries) Adm. O. = Orally I.V. = Intravenously	Roentgenological Findings R = Raref'action	X-Radiation or Neutron Radiation and Dates	Dates	Number	Total Amount of Blood in c.c.	LN = Lymph Node S = Spleen L = Liver I = Increased D = Decreased U = Unchanged } Refers to Change in Size	Min. and Max. Levels Hb (%) Sahli	Min. and Max. Levels WBC/Cu. mm. in 1000's	Clinically and Hematologically Normal for a Period of 1 Year	General Condition of Patient on Mar. 15, 1941	Date of Death	Hours Between Death and Autopsy	Gross Findings (Weight in Grams)	Microscopical Findings	Peripheral Blood = PB Excretions = E Tissue = T	Number
15	16	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Leukemoid Reactions																
a. Myeloid (Associated with Neuroblastoma)																
11/17/39 to 11/29/39 8.3 (O.)	R—most bones	12/4/39 to 12/7/39 1100 r				LN—U S—U L—I (12 cm.)	65 to 85	9 to 13			12/8/39	18	Neuroblastoma with generalized metastases in most organs	Typical microscopic findings	T	96
b. Myeloid (Associated with Polycythemia)																
2/26/40 to 8/10/40 29.12 (O.)						LN—U S—D (6 cm.) L—D (2 cm.)	110 to 115	15 to 83	Yes	Excellent					P B E	97
c. Lymphoid (Associated with Leukosarcoma)																
1/9/41 to 3/4/41 6.9 (I.V.) 7.5 (O.)						Ascites and edema of legs entirely disappeared	81 to 85	8 to 30		Excellent						98
d. Monocytoid (Associated with (99) Chloroma and (100) Diffuse Miliary Tuberculosis)																
1/2/41 to 3/8/41 14.08 (I.V.) 1.7 (O.)						LN—D S—not palpable L—not palpable Sub. masses disappeared. Protrusion of eyes unchanged	85 to 111	3 to 6			3/27/41		Liver and spleen normal size. Kidneys and adrenal surrounded with tumor. All nodes 3× normal size. Retrobulbar masses present	Liver—not infil.; spleen—fibrotic marked infil. of heart, kidneys, adrenals, G.I. tract, pancreas, pituitary gland and brain. Marrow—replaced by round cells	T	99
4/5/39 to 4/26/39 7.3 (O.)						LN—U S—U L—U	50 to 59	12 to 24			6/ 6/39	6	Splenomegaly	Diffuse miliary tuberculosis of peritoneum, spleen, marrow, liver, adrenals, lymph nodes, but not lungs		100

TABLE II

Myeloid Leukemia

	Clinical Data Previous to Administration of Radio-Phosphorus														Treatment				
						Physical and Lab. Findings on Admis.						Biopsy			P^{32}	Radiation	Transfusion		
	Name and Number	Sex and Age in Years	Date of Admission	Chief Complaints and Duration of Chief Complaints on Admission	A. Diagnosis and B. Treatment Previous to Admission	Characteristics of Peripheral Lymph Nodes	Extension of Spleen Below Costal Margin in Cm.	Extension of Liver Below Costal Margin in Cm.	Other Findings	Hb (%) Sahli	WBC/Cu. Mm. in Thous.	M = Sternal Marrow L = Lymph Node R = Rib Marrow S = Skin Hyper = Hyperplastic	Chemistry and Serology, etc.	Roentgenological Findings R = Rarefaction	Dates and Total Dosages of Radio-Phosphorus (in Millicuries) Administered O. = Orally I.V. = Intravenously	X-Radiation or Neutron Radiation and Dates	Dates	Number	Total Amount of Blood in c.c.
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Acute	5 Chr.	M 55	5/ 3/39	1. Tiredness—2 mo.	A. None B. No R				Petechiae over skin of chest. Pitting edema—ankles	41	14				5/23/39 4.88 (O.)		5/9/39	1	500
	6 Far.	M 40	4/25/40	1. Intermittent abdominal pains } 6 wks. 2. Weakness 3. Fever and headache receding } 2 wks.	A. None B. No R	Axillary nodes slightly enlarged	2	4	Hemorrhagic ulceration left angle of mouth	50	18	M. hyper. (myeloblasts predominate)	Wass. blood culture } neg.		4/28/40 to 7/3/40 24.11 (O.)		4/30/40 to 7/ 3/40	10	5000
	7 Dan.	M 5	1/19/40	1. Pallor 2. Enlarged abdomen } 3 wks. 3. Fever 4. Headache	A. None B. No R	General enlargement	12		Pallor	42	265	M. hyper. (90% myelocytes)	Wass. Tuberculin } neg.	R of most bones	1/22/40 to 2/ 1/40 2.0 (O.)		1/22/40 to 2/ 1/40	3	600
	8 Mar.	M 7	3/ 7/40	1. Listlessness 2. Fever 3. Enlargement of axillary, cervical and inguinal nodes } 2 mo.	A. None B. No R	General enlargement (1 cm.)	1	4	Tonsils large and hyperemic	74	89		Wass. Tuberculin Heterophile agg. } neg.		3/10/40 to 7/11/40 11.84 (O.)	5/25/40 to 6/8/40 350 r	3/31/40	1	500
	9 Pra.	F 61	11/17/38	1. Weakness 2. Headache 3. Diaphoresis 4. Stomatitis } 4 mo.	A. None B. No R				Gums swollen, pale, and bleeding. Pallor	47	9	M. hyper. (90% myelocytes)			11/30/38 to 12/11/38 15.36 (O.)		11/17/38 to 12/ 4/38	4	2000

TABLE II (*Continued*)

TABLE II (*Continued*)

Acute	10 Ric.	M 67	1/13/40	1. Weakness 2. Necrotic gums } 3 mo.	A. None B. No R	Cervical nodes (2×)	2	1	Gums hyperplastic, pale, and necrotic. Pallor	44	108				1/16/40 to 1/17/40 14.2 (O.)				
	11 Str.	F 42	4/23/40	1. Weakness—3 mo.	A. None B. No R	Shotty				37	32		Wass.—neg.		4/23/40 to 5/22/40 5.0 (O.)		4/23/40 to 4/28/40	2	1000
	12 Wel.	F 40			A. B.										7/ 2/38 to 7/30/38 5.96 (O.)				
Chronic	13 Ani.	F 48	2/18/41	1. Tiredness 2. Diarrhea 3. Vomiting } 2 mo.	A. Leukemia Jan. 1941 B. No R		7			91	117				2/19/41 3.0 (O.)				
	14 Bea.	M 45	5/ 6/40	1. Intermittent pain in upper left and lower right quadrant and headache } 4 yr.	A. None B. No R		8	4	Mass in right, lower quadrant	53	164	M. hyper. (50% myelocytes)			5/22/40 to 9/25/40 .87 (I.V.) 14.91 (O.)				
	15 Bram.	F 45	4/28/39	1. Weakness 2. Loss of weight 3. Ecchymosis 4. Enlarged abdomen } 1 yr.	A. Leukemia Nov. 1938 B. X-radiation 1750 r	General enlargement	5		Pigmentation of skin over splenic area	84	100				4/29/39 to 11/13/39 35.04 (O.)		12/ 8/39 to 12/28/39	4	2000
	16 Brat.	F 21	7/20/38	1. Weakness—2 mo.	A. None B. No R	Shotty	4		Pallor	63	195				7/20/38 to 9/ 8/39 41.65 (O.)				
	17 Cole	M 23	5/23/40	1. Weakness } 1 yr. 2. Diaphoresis 3. Abdominal pain } 2 mo. 4. Headache	A. None B. No R	Postcervical and axillary nodes. Shotty	Not palp.	Not palp.	Slight gingivitis	81	148	M. hyper. (myeloid)			5/27/40 to 1/ 8/41 19.0 (O.)				
	18 Cur.	F 18	6/15/39	1. Weakness—3 yr. 2. Fever 3. Bone pains } 2 mo. 4. Night sweats	A. Leukemia Apr. 1936 B. X-radiation. Many courses		3		Pallor	30	470		Wass.—neg. B.M.R. (−2)		9/ 6/39 to 9/16/39 14.77 (O.)		9/ 6/39 to 9/16/39	3	1500
	19 Ebe.	M 39	1/20/39	1. Weakness 2. Night sweats 3. Headache } 2 yr.	A. Leukemia Feb. 1937 B. X-radiation. 3 courses		3		Pallor	90	128				1/24/39 to 9/ 9/39 60.0 (O.)	8/ 7/39 to 8/19/39 750 r	9/ 8/39 to 9/12/39	2	1000
	20 Fla.	F 35	1/13/41	1. Fatigue 2. Headache 3. Diffuse joint pains } 2 yr.	A. Leukemia Jan. 1939 B. X-radiation 2/39 to 12/40 3000 r		2	0.5		82	186				1/14/41 to 1/31/41 6.7 (I.V.)				

TABLE II (*Continued*)

	Clinical Data Previous to Administration of Radio-Phosphorus					Physical and Lab. Findings on Admis.						Biopsy			Treatment				
	Name and Number	Sex and Age in Years	Date of Admission	Chief Complaints and Duration of Chief Complaints on Admission	A. Diagnosis and B. Treatment Previous to Admission	Characteristics of Peripheral Lymph Nodes	Extension of Spleen Below Costal Margin in Cm.	Extension of Liver Below Costal Margin in Cm.	Other Findings	Hb (%) Sahli	WBC/Cu. Mm. in Thous.	M = Sternal Marrow L = Lymph Node R = Rib Marrow S = Skin Hyper = Hyperplastic	Chemistry and Serology, etc.	Roentgenological Findings R = Rarefaction	P^{32} Dates and Total Dosages of Radio-Phosphorus (in Millicuries) Administered O. = Orally I.V. = Intravenously	Radiation X-Radiation or Neutron Radiation and Dates	Transfusion Dates	Number	Total Amount of Blood in c.c.
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Chronic	21 Gir.	M 41	12/28/40	1. Shortness of breath 2. Perspiration 3. Abdominal pain } 6 mo.	A. Leukemia Oct. 1940 B. No R	Shotty	7	0.5	Dyspnea	55	362				12/28/40 to 2/13/41 8.95 (I.V.)				
	22 Hall	F 49	10/ 2/40	1. Headache 2. Irritability 3. Abdominal pain } 4 mo.	A. Leukemia Aug. 1940 B. Small amount of X-radiation	Shotty	14	1		84	336				10/ 7/40 to 12/27/40 16.9 (O.)				
	23 Hay.	F 57	1/ 9/41	1. Fatigue—9 mo.	A. Leukemia Sept. 1940 B. No R	Shotty	6			91	132	M. hyper. (immature myeloid cells predominate)			1/ 9/41 to 1/28/41 6.0 (I.V.)				
	24 Her.	M 60	11/27/39	1. Weakness 2. Enlarged abdomen 3. Swollen ankles } 2–6 mo.	A. None B. No R		To iliac crest	To iliac crest	Pallor	43	551	M. hyper. (90% myelocytes)			12/ 9/39 to 12/24/39 21.26 (O.)		12/ 5/39	1	500
	25 Hin.	M 21	10/ 7/39	1. None	A. Leukemia Sept. 1937 B. Fowler's solution. X-radiation 1500 R. Also Heublein technic	Shotty	8			33	200	M. hyper. (90% immature myeloid cells)		Both tibii diffuse R	10/13/39 to 10/20/39 18.14 (O.)		9/ 1/39 to 10/10/39	4	800

TABLE II (*Continued*)

Chronic	26 Iff.	F 74	7/29/40	1. Weakness 2. Fatigue	A. Leukemia Jan. 1939 B. X-radiation 11/39 to 7/40 1000 r		6	3	Pallor	74	23	M. hyper. (myeloid infiltration)			7/30/40 to 1/22/41 18.3 (O.)				
	27 Ken.	M 21	11/ 4/38	1. Weakness—1 mo.	A. Leukemia Nov. 1938 B. No R	Axillary nodes enlarged	8	1		70	210	M. hyper. (myeloid)			11/28/38 to 6/13/39 10.72 (O.)				
	28 Kli.	M 31	5/13/40	1. Weakness 2. Loss of weight 3. Diaphoresis 4. Cramps in calves } 1 yr.	A. Leukemia Dec. 1939 B. X-radiation 1500 r	Shotty	4	1		76	103	M. hyper. (80% myeloid cells)			6/13/40 to 11/23/40 1.95 (I.V.) 17.0 (O.)				
	29 Kre.	M 11	7/14/39	1. Weakness 2. Pain in groin 3. Fever } 3 mo.	A. Leukemia May 1939 B. X-radiation 1000 r	Shotty	2		Petechiae in oral mucous membrane	57	315				7/14/39 to 2/ 4/41 28.0 (O.)	10/ 7/39 to 11/15/39 800 r	7/14/39 to 2/ 4/41	5	2100
	30 LaV.	F 44	10/25/38	1. Weakness } 5 yr. 2. Leukemids 3. Diaphoresis } 2 yr. 4. Swollen ankles	A. Leukemia Sept. 1935 B. X-radiation. Many courses	Inguinal nodes enlarged (2×)			(6/10/35 First admis. 10/25/38 Second admis.	75 100	208) 13	M. hyper. (normal diff. Dec. 1939)			1/ 4/39 to 2/17/41 21.72 (O.)				
	31 Loh.	M 33	7/21/38	1. Weakness 2. Abdominal pain 3. Splenic infarcts—Second admission	A. Leukemia 1935 B. Fowler's solution. X-radiation 5000 r	General enlargement (2×)	6	5	Pallor. Hemorrhoids	40	147		Wass.—neg. B.M.R. (+47)		8/ 1/38 to 8/20/38 15.87 (O.)		8/ 2/38	1	500
	32 Loo.	M 46	10/16/40	1. Weakness 2. Loss of weight 3. Pain in upper abdomen } 1 yr. 4. Bone pains in hands and attacks of diarrhea	A. Leukemia Feb. 1940 B. X-radiation 1050 r	Shotty	Just palp.	Just palp.		92	77			R—bones of hands	10/16/40 to 2/18/41 25.4 (O.)				
	33 Mar.	F 11	4/12/40	1. Tiredness—2 mo.	A. None B. No R	Shotty	4			88	125	M. hyper. (myeloid)		R—all bones	4/13/40 to 2/19/41 17.17 (O.)				
	34 Mas.	M 46	11/18/40	1. Weakness 2. Fatigue 3. Headache } 2 yr.	A. Leukemia Sept. 1938 B. X-radiation 3/11/39 to 9/17/40 2000 r	Shotty	6	Not palp.		100	159				11/18/40 to 1/31/41 4.7 (I.V.) 8.7 (O.)				

TABLE II (*Continued*)

Clinical Data Previous to Administration of Radio-Phosphorus

Treatment

	Name and Number	Sex and Age in Years	Date of Admission	Chief Complaints and Duration of Chief Complaints on Admission	A. Diagnosis and B. Treatment Previous to Admission	Physical and Lab. Findings on Admis.: Characteristics of Peripheral Lymph Nodes	Extension of Spleen Below Costal Margin in Cm.	Extension of Liver Below Costal Margin in Cm.	Other Findings	Hb (%) Sahli	WBC/Cu. Mm. in Thous.	Biopsy: M = Sternal Marrow, L = Lymph Node, R = Rib Marrow, S = Skin; Hyper = Hyperplastic	Chemistry and Serology, etc.	Roentgenological Findings: R = Rarefaction	P^{32}: Dates and Total Dosages of Radio-Phosphorus (in Millicuries) Administered; O. = Orally, I.V. = Intravenously	Radiation: X-Radiation or Neutron Radiation and Dates	Transfusion: Dates	Transfusion: Number	Transfusion: Total Amount of Blood in c.c.
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Chronic	35 Mon.	M 37	6/27/40	1. Weakness 2. Abdominal pains 3. Headache — 4 mo.	A. Leukemia May 1940 B. No R	Shotty	Not palp.	3		90	64	M. hyper. (myeloid)			6/27/40 to 1/23/41 32.0 (O.)				
	36 Mor.	F 38	9/18/38	1. Weakness 2. Nausea and vomiting 3. Bleeding gums — 15 mo.	A. Leukemia June 1937 B. X-radiation Many courses		7		Pallor	64	275				9/21/38 to 9/10/39 60.22 (O.)				
	37 Nut.	M 57	5/ 3/40	1. Weakness 2. Splenomegaly — 8 mo.	A. Leukemia Jan. 1940 B. No R	General enlargement slight. Shotty	22		Pallor	68	380	M. hyper. (myeloid)			5/ 2/40 to 2/18/41 9.7 (I.V.) 25.52 (O.)				
	38 Pac.	M 33	7/31/39	1. Weakness 2. Epistaxis 3. Enlarged abdomen 4. Bleeding gums — 2–3 yr.	A. Leukemia 1936 B. X-radiation 4500 r	General enlargement (3×)	18		Pallor	70	76				7/31/39 to 8/ 6/39 10.32 (O.)				
	39 Par.	M 51	5/14/40	1. Weakness 2. Diaphoresis 3. Anorexia 4. Loss of weight — 9 mo.	A. Leukemia May 1940 B. No R	Shotty	20		Crepitant râles throughout both lungs. Pitting edema—ankles	74	335				5/14/40 to 3/ 7/41 4.41 (I.V.) 26.0 (O.)				
	40 Pol.	F 36	2/19/41	1. Weakness—5 yr.	A. Leukemia Jan. 1936 B. X-radiation 15 courses	Shotty	15	2	Mitral heart disease	90	37				2/25/41 2.3 (I.V.)				
	* 41 Rov.	M 52			A. B.										2/ 1/38 to 8/29/38 90.72 (O.)				

TABLE II (*Continued*)

* 41 Rov.	M 52			A. B.											2/ 1/38 to 8/29/38 90.72 (O.)					

TABLE II (*Continued*)

Chronic	A. 42 Smi.	F 40	7/15/39	1. Weakness—2 yr. 2. Swollen ankles—3 mo.	A. Leukemia 1937 B. X-radiation 3000 r	Shotty				80	155				7/18/39 to 6/19/40 52.8 (O.)					
	J. 43 Smi.	M 33	5/24/39	1. Weakness—2 yr.	A. Leukemia 1937 B. X-radiation Many courses		1			92	380	M. hyper. (myelocytes predominate)			5/31/39 to 2/12/40 68.45 (O.)	3/13/40 to 4/20/40 300 n				
	44 Sor.	M 61	5/13/40	1. Weakness—3 wks. First admission	A. Leukemia Aug. 1937 B. Fowler's solution. X-radiation Unknown amounts		8	4		85	209				5/17/40 to 11/ 9/40 20.85 (O.)					
	45 Tha.	M 51	6/15/39	1. Weakness 2. Dyspnea } 2 yr.	A. Leukemia July 1937 B. X-radiation Many courses	Shotty	6		Left fundal hemorrhage. Rt. leg 3" shorter due to spontaneous fracture 1931	72	97				10/24/39 to 5/16/40 1.14 (I.V.) 25.0 (O.)					
	46 Tho.	M 65	9/20/39	1. Weakness 2. Dyspnea } 2 mo. 3. Ankle edema	A. Leukemia Aug. 1939 B. Fowler's solution	General enlargement (2×)	4	1	Left testis 8×4×4 cm.	30	184	M. hyper. (myelocytes predominate)	Wass.—neg. B.M.R. (+42)		10/18/39 to 2/24/40 28.7 (O.)					
	47 Wal.	M 31	11/15/39	1. Periodic weakness for 23 mo.	A. Leukemia Jan. 1938 B. Fowler's solution. X-radiation Many courses	Shotty				110	14				12/ 9/39 to 2/20/40 23.06 (O.)					
	48 Wat.	M 42	12/17/38	1. Weakness—6 mo. 2. Soft stools—4 yr. 3. Pain in upper left quadrant—1 wk.	A. Leukemia Feb. 1938 B. X-radiation 7000 r	Axillary nodes enlarged (3×)	9			52	256				3/17/39 to 5/ 3/39 35.77 (O.)					
	49 Wil.	F 12	7/10/40	1. Pallor and purpura 2. Loss of weight 3. Hiccoughs and cramps in legs } 5 mo.	A. Leukemia May 1940 B. X-radiation 250 r		8	2	Skin and hair very dry	60	182				7/10/40 to 12/ 2/40 25.3 (O.)	12/12/40 to 12/14/40 120 r				
	50 Yat.	F 40	8/27/40	1. Weakness 2. Deep boring bone pains in pelvis, back and sternum	A. Leukemia Mar. 1939 B. X-radiation since Mar. 1939		1	1		94	15				8/27/40 to 12/ 5/40 28.0 (O.)					

* Published previously.

TABLE II (*Continued*)

Clinical Data After Administration of Radio-Phosphorus

	Name and Number	Sex and Age in Years	Date of Admission	Physical and Lab. Findings: LN = Lymph Node, S = Spleen, L = Liver; I = Increased, D = Decreased, U = Unchanged; Refers to Change in Size After That Found on Admission	Min. and Max. Levels: Hb (%) Sahli	Min. and Max. Levels: WBC/Cu. Mm. in Thous.	Remissions: Partial — Patient Essentially Normal Clinically. Associated with a Distinct Improvement in Hb and WBC Levels for Periods of A = 3 Mos., B = 6 Mos., C = 1 Yr.	Remissions: Complete — Patient Clinically and Hematologically Normal for Periods of A = 3 Mos., B = 6 Mos., C = 1 Yr.	General Condition of Patient as of March 15, 1941	Postmortem Findings: Date of Death	Postmortem Findings: Hours Between Death and Autopsy	Postmortem Findings: Gross Findings (Weights in Grams)	Postmortem Findings: Microscopical Findings	Radio-Phosphorus Studies: Peripheral Blood = P.B. Excretions = E. Tissue = T.	Number
	1	2	3	20	21	22	23	24	25	26	27	28	29	30	31
Acute	5 Chr.	M 55	5/ 3/39	LN—U S—U L—U	No change	No change				5/27/39	1½	Liver—4050; spleen—900. Marrow hyperplastic	All tissues except pancreas and adrenal infiltrated with myeloblasts. Spotty infiltration of kidneys. Myeloid hyperplasia present in marrow and nodes		5
	6 Far.	M 40	4/25/40	LN—U S—U L—U	20 to 50	18 to 47				7/ 8/40	12½	Spleen—250; kidneys—800. General enlargement of all lymph nodes	Marked infiltration of G.I., mucosa, submucosa and kidneys. Diffuse infiltration of lung and lymph nodes. Marrow hyperplastic	T.	6
	7 Dan.	M 5	1/19/40	LN—U S—U L—U	42 to 60	43 to 265				3/ 8/40					7
	8 Mar.	M 7	3/ 7/40	LN—U S—U L—U	33 to 74	7 to 89				7/16/40					8
	9 Pra.	F 61	11/17/38	LN—U S—U L—U	45 to 48	9 to 70				12/17/38					9
	10 Ric.	M 67	1/13/40	LN—U S—U L—U	34 to 44	108 to 150				1/17/40	4	Liver—1600; spleen—900. Marrow red and hyperplastic	Typical infiltration of spleen, liver, nodes and marrow	P.B. T.	10
	11 Str.	F 42	4/23/40	LN—U S—U L—U	37 to 38	21 to 32				5/22/40					11
	12 Wel.	F 40								7/31/38	5	Liver, normal size; spleen 2×. Nodes not enlarged	Diffuse myeloid infiltration in fatty liver, G.I., submucosa and hematopoietic organs	E. T.	12

TABLE II (*Continued*)

										7/31/38	3	Liver, normal size; spleen 2×. Nodes not enlarged	Diffuse myeloid infiltration in fatty liver, G.I., submucosa and hematopoietic organs	E. T.	12

TABLE II (*Continued*)

Chronic	13 Ani.	F 48	2/18/41	LN—U S—U L—U	78	84			Good						13
	14 Bea.	M 45	5/6/40	LN—U S—D (1 cm.) L—D (not palp.)	76 to 116	7 to 100	B		Excellent					P.B. E.	14
	15 Bram.	F 45	4/28/39	LN—U S—I (20 cm.) L—U	59 to 65	16 to 165				1/28/40					15
	16 Brat.	F 21	7/20/38	LN—U S—D L—U	38 to 82	4 to 183	C			1/ 6/40	1	Liver—2180; spleen—2160. Marrow gray-red	Large multinucleated atypical myeloid cells associated with megakaryocytes in marrow, nodes, spleen and liver but not in kidneys, G.I., adrenal, heart, or pancreas	T.	16
	17 Cole	M 23	5/23/40	LN—U S—U L—U	85 to 114	38 to 136	B		Excellent					E.	17
	18 Cur.	F 18	6/15/39	LN—U S—U L—U	30 to 40	370 to 470				9/21/39	5	Liver—2860; spleen—3000. Marrow pale gray and abundant	Myeloid infiltration of all organs including submucosa of G.I. tract	T.	18
	19 Ebe.	M 39	1/20/39	LN—I S—I L—U	40 to 98	32 to 166	B			9/15/39	3	Liver—2700; spleen—2520, firm. Marrow gray-red	Myeloid infiltration of all organs including submucosa of G.I. tract	P.B. E.	19
	20 Fla.	F 35	1/13/41	LN—U S—U L—U	70 to 82	161 to 186			Good					P.B.	20
	21 Gir.	M 41	12/28/40	LN—U S—U L—U	55 to 59	280 to 425				3/12/41		(Against advice patient had 4 teeth pulled followed by uncontrollable bleeding)		P.B.	21
	22 Hall	F 49	10/ 2/40	LN—U S—D (2 cm.) L—U	67 to 114	67 to 476	B		Excellent						22
	23 Hay.	F 57	1/ 9/41	LN—U S—D (1 cm.) L—U	80 to 91	76 to 130			Excellent					P.B.	23
	24 Her.	M 60	11/27/39	LN—U S—U L—U	43 to 45	500 to 550				1/ 4/40	16	Liver—1400; spleen—1400, firm. Marrow gray-red	Myeloid infiltration of all organs. Localized infiltration of left adrenal measuring 5 mm. in diam.	T.	24
	25 Hin.	M 21	10/ 7/39	LN—I S—I L—I	31 to 33	106 to 200				10/22/39					25

TABLE II (*Continued*)

Clinical Data After Administration of Radio-Phosphorus

Chronic

Name and Number	Sex and Age in Years	Date of Admission	Physical and Lab. Findings: LN = Lymph Node; S = Spleen; L = Liver; I = Increased; D = Decreased; U = Unchanged; Refers to Change in Size After That Found on Admission	Min. and Max. Levels: Hb (%) Sahli	Min. and Max. Levels: WBC/Cu. Mm. in Thous.	Remissions: Partial — Patient Essentially Normal Clinically. Associated with a Distinct Improvement in Hb and WBC Levels for Periods of A = 3 Mos., B = 6 Mos., C = 1 Yr.	Remissions: Complete — Patient Clinically and Hematologically Normal for Periods of A = 3 Mos., B = 6 Mos., C = 1 Yr.	General Condition of Patient as of March 15, 1941	Date of Death	Hours Between Death and Autopsy	Postmortem Findings: Gross Findings (Weights in Grams)	Postmortem Findings: Microscopical Findings	Radio-Phosphorus Studies: Peripheral Blood = P.B. Excretions = E. Tissue = T.	Number
1	2	3	20	21	22	23	24	25	26	27	28	29	30	31
26 Ilf.	F 74	7/29/40	LN—U S—D (1 cm.) L—D (not palp.)	71 to 86	12 to 23			Good						26
27 Ken.	M 21	11/ 4/38	LN—D (not palp.) S—D (not palp.) L—D (not palp.)	70 to 110	8 to 210		2½ years	Excel-lent					P.B. E.	27
28 Kli.	M 31	5/13/40	LN—U S—D (not palp.) L—D (not palp.)	79 to 105	30 to 146	B		Excel-lent					P.B. E.	28
29 Kre.	M 11	7/14/39	LN—U S—D (not palp.) L—D (not palp.)	57 to 116	4 to 315		C		2/16/41					29
30 LaV.	F 44	10/25/38	LN—U S—U L—U	75 to 106	4 to 21		2 years	Excel-lent						30
31 Loh.	M 33	7/21/38	LN—D S—I (8 cm.) L—D (3 cm.)	40 to 42	2 to 147	B			9/22/38	1½	Liver—2650; spleen—3100; kidneys—450. Marrow gray and soft. Slough on arm due to vaccination	Myeloid infiltration of heart, muscle, spleen, liver, lymph nodes, and striated muscle. Marrow almost solidly packed with myeloblasts. No kidney infiltration		31
32 Loo.	M 46	10/16/40	LN—U S—U L—U	81 to 99	20 to 120			Excel-lent						32
33 Mar.	F 11	4/12/40	LN—U S—U L—U	88 to 109	125 to 23	C		Excel-lent						33

TABLE II (*Continued*)

Chronic	34 Mas.	M 46	11/18/40	LN—U S—D (4 cm.) L—U	100 to 78	148 to 53			Excellent					P.B.	34
	35 Mon.	M 37	6/27/40	LN—U S—U L—D (1 cm.)	87 to 98	8 to 64		A	Excellent						35
	36 Mor.	F 38	9/18/38	LN—U S—U L—U	16 to 64	4 to 275	A 2 occasions			10/18/39	10	Liver—1900; spleen—1100. Marrow red	Myeloid infiltration of many organs, but not kidney or adrenals. Infarct of spleen. Myeloblastic hyperplasia of marrow	T.	36
	37 Nut.	M 57	5/ 3/40	LN—U S—D (4 cm.) L—U	66 to 87	76 to 380			Excellent					T.	37
	38 Pac.	M 33	7/31/39	LN—U S—U L—U	65 to 70	12 to 138				8/11/39	12	Liver—2900; spleen—2640. Marrow red and hyperplastic	Myeloid infiltration of all organs, except kidney and brain		38
	39 Par.	M 51	5/14/40	LN—U S—D (1 cm.) L—U	70 to 99	44 to 335			Good						39
	40 Pol.	F 36	2/19/41	LN—U S—U L—U	93	23			Good						40
	* 41 Rov.	M 52								9/28/38	18	Liver—2010; spleen—780. Marrow red and hyperplastic; multiple white patches on pleura	Diffuse miliary tuberculosis was observed. Little leukemic infiltration microscopically	T.	41
	A. 42 Smi.	F 40	7/15/39	LN—U S—U L—U	60 to 65	5 to 155		B		8/23/40					42
	J. 43 Smi.	M 33	5/24/39	LN—U S—I (20 cm.) L—I (6 cm.)	40 to 83	17 to 215	B			5/11/40		Spleen—455; liver—3310; kidneys—449. Bronchial nodes enlarged, soft, gray. Many infarcts on spleen		T.	43
	44 Sor.	M 61	5/13/40	LN—U S—U L—U	30 to 80	169 to 640				11/13/40					44
	45 Tha.	M 51	6/15/39	LN—U S—I (16 cm.) L—U	45 to 63	6 to 97	A			6/13/40				P.B. E.	45
	46 Tho.	M 65	9/20/39	LN—U S—U L—U	27 to 35	9 to 184				3/23/40	2	Liver—2300; spleen—390. Marrow red and hyperplastic	Myeloid infiltration of all organs except kidneys and pancreas. Diffuse miliary tuberculosis involving lungs, liver, spleen and lymph nodes. Marrow—myeloblastic hyperplasia	T.	46

TABLE II (*Continued*)

Clinical Data After Administration of Radio-Phosphorus

Chronic

Name and Number	Sex and Age in Years	Date of Admission	Physical and Lab. Findings: LN = Lymph Node, S = Spleen, L = Liver; I = Increased, D = Decreased, U = Unchanged; Refers to Change in Size After That Found on Admission	Min. and Max. Levels: Hb (%) Sahli	Min. and Max. Levels: WBC/Cu. Mm. in Thous.	Remissions: Partial — Patient Essentially Normal Clinically. Associated with a Distinct Improvement in Hb and WBC Levels for Periods of A = 3 Mos., B = 6 Mos., C = 1 Yr.	Remissions: Complete — Patient Clinically and Hematologically Normal for Periods of A = 3 Mos., B = 6 Mos., C = 1 Yr.	General Condition of Patient as of March 15, 1941	Date of Death	Hours Between Death and Autopsy	Postmortem Findings: Gross Findings (Weights in Grams)	Postmortem Findings: Microscopical Findings	Radio-Phosphorus Studies: Peripheral Blood = P.B. Excretions = E. Tissue = T.	Number
1	2	3	20	21	22	23	24	25	26	27	28	29	30	31
47 Wal.	M 31	11/15/39	LN—U S—I (12 cm.) L—I (2 cm.)	60 to 93	8 to 82				5/18/40					47
48 Wat.	M 42	12/17/38	LN—U S—I (22 cm.) L—U	38 to 70	6 to 256				7/12/39	6	Liver 15×31×15 cm.; spleen 10×19×19 cm. Retroperitoneal gland enlarged 2×	Myeloid infiltration of all organs except kidneys. Bladder and submucosa of G.I. tract densely infiltrated	T.	48
49 Wil.	F 12	7/10/40	LN—U S—U L—U	67 to 88	230 to 50				12/21/40					49
50 Yat.	F 40	8/27/40	LN—U S—U L—U	94 to 48	15 to 40				12/27/40		Bone pains continued until death			50

Because of the findings obtained from absorption and autopsy studies, we feel at the present time that frequent administrations of small doses (0.5 to 2 Mc) of radio-phosphorus to patients with leukemia are preferable to infrequent large doses. It is known that radio-phosphorus can reach nearly every cell in the body and that it concentrates in those cells with active metabolic rates.[15, 26] There is no evidence that cells can distinguish radio-phosphorus (atomic weight 32) from ordinary non-radioactive phosphorus (atomic weight 31). In tables 7 and 8 it can be noted that most of the doses given orally were of the same order of magnitude, and this was true with those given intravenously. The physiological function of normal cells was probably altered by these amounts of irradiation and therefore these doses are said to be "therapeutic" in nature, in contrast to "tracer" doses which are so small that the emitted radiation would not alter cellular physiology. Since the dosages of P^{32} administered to the normal individuals, myeloid and lymphoid leukemic patients were similar, the results in most instances can be discussed comparatively.

3. Tolerance.

Radio-phosphorus is well tolerated by humans and animals. Multiple doses have been administered both orally and intravenously to over 300 persons with various disease processes and in none has there been any untoward reaction which might reasonably be ascribed to the radio-phosphorus, such as "radiation" nausea, vomiting, headache and weakness. One notable effect has been that of a marked increase in appetite for one or two days following the administration of radio-phosphorus.

B. Patients.

The cases reported, with one exception, are those of patients who were treated at the Crocker Radiation Laboratory or in hospitals near the Laboratory. The large number of patients who were treated elsewhere could not be followed closely and therefore are not reported at this time. The patients with leukemia were classified according to the predominating cell in the blood stream and to the acuteness or chronicity of the process. Most of the patients who were treated with radio-phosphorus had high white blood cell levels. Eight patients with leukemia, whose cases have been previously recorded [20, 22, 35] are included in this report. The patients with leukemoid reactions are classified according to the primary etiological process. Through rare good fortune, studies on the rates of absorption and excretion of radioactive phosphorus were made on four healthy, robust normal men with recently healed fractures, all of whom had received the same type and quantity of food for a period of from one to eight weeks, and each of whom had a single regular bowel movement daily. These persons were particularly valuable because they all had had the same dietary phosphorus intake for weeks before, and during the period of study.

C. Technic of Diagnosis and of Radioactivity Assays.

Table III

Lymphoid Leukemia

Acute

Clinical Data Previous to Administration of Radio-Phosphorus														Treatment				
					Physical and Lab. Findings on Admis.						Biopsy			P^{32}	Radiation	Transfusion		
Name and Number	Sex and Age in Years	Date of Admission	Chief Complaints and Duration of Chief Complaints on Admission	A. Diagnosis and B. Treatment Previous to Admission	Characteristics of Peripheral Lymph Nodes	Extension of Spleen Below Costal Margin in Cm.	Extension of Liver Below Costal Margin in Cm.	Other Findings	Hb (%) Sahli	WBC/Cu. Mm. in Thous.	M = Sternal Marrow L = Lymph Node R = Rib Marrow S = Skin Hyper = Hyperplastic	Chemistry and Serology, etc.	Roentgenological Findings R = Rarefaction	Dates and Total Dosages of Radio-Phosphorus (in Millicuries) Administered O. = Orally I.V. = Intravenously	X-Radiation or Neutron Radiation and Dates	Dates	Number	Total Amount of Blood in c.c.
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
51 Ande.	F 4	1/27/41	1. Weakness 2. Pallor 3. Gen. lymphadenopathy — 2 mo.	A. Acute leukopenic lymphoid leukemia B. Transfusion	Gen. enlargement all approx. 1cm. in dia.	1	1	1. Scattered purpura	87	3	M—hypoplastic (lymphoid infiltration) L—lymphoid hyper.			2/13/41 to 2/17/41 2 Mc. (I.V.)	1/27/41 to 2/24/41 30 n	2/25/41 to 2/26/41	2	500
52 Andr.	F 1½	9/11/40	1. Pallor 2. Irritability 3. Distended abdomen — 2 mo.	A. Peritonitis B. No R	Gen. enlargement	4	5	1. Ascites	30	78	M—hyper. (60% lymphocytes, 30% lymphoblasts)			9/15/40 1 Mc. (I.V.)		9/12/40 to 9/14/40	2	400
53 Bel.	M 37	7/15/39	1. Weakness 2. Diaphoresis 3. Loss of weight—2 wks. — 4 wks.	A. None B. No R	Small, shotty	3		1. Purpura skin of legs	25	126				7/31/39 to 8/26/39 20.35 (O.)		6/30/39 to 8/28/39	9	4500
54 Bor.	M 2	4/ 5/39	1. Lethargy, pallor 2. Purpura 3. Fever 4. Enlarged lymph nodes — 1 mo.	A. None B. No R	Gen. enlargement		3	1. Gen. purpura	30	26			R—long bones	5/26/39 to 7/ 9/39 5.49 (O.)		5/26/39 to 7/ 9/39	6	900
55 Bri.	F 8	12/10/40	Following "flu" in October, 1939, patient complained of weakness only	A. Leukemia Jan. 1940 B. X-radiation	Gen. enlargement, shotty	14	2	1. Gen. purpura 2. Bleeding gums	40	200		Wass.—neg.	R—all bones	12/17/40 1.9 (I.V.)				
56 Cre.	F 3	11/25/40	1. Irritability 2. Fever 3. Skin sensitivity 4. Abdominal pain — 1 mo.	A. None B. No R	Shotty, firm	2	1	1. Scattered purpuric spots	41	3	M—hyper. (60% lymphocytes, 35% lymphoblasts)		No abnormal findings		12/18/40 to 1/27/41 45 n	11/27/40 to 12/18/40	8	1200

Table III (*Continued*)

TABLE III (*Continued*)

Acute	57 Fie.	M 8	11/23/40	1. Pallor 2. Weakness 3. No appetite 4. Attacks of vomiting, fever — 1 mo.	A. Leukemia Oct. 1940 B. 3 transfusions	Gen. enlargement, shotty	2	2		67	40				11/24/40 to 11/29/40 2.0 (I.V.)		10/24/40 to 2/23/41	6	2000
	58 Gre.	M 45	4/17/40	1. Weakness 2. Enlarged peripheral nodes 3. Diaphoresis 4. Dyspnea — 2 mo.	A. None B. No R	Gen. enlargement (2×)	4	8	1. Enlarged tonsils 2. Gen. purpura	47	11				4/18/40 to 5/15/40 19.65 (O.)		4/24/40 to 5/18/40	7	3500
	59 Her.	M 4	7/12/40	1. Listlessness — 5 mo. 2. Anorexia, pallor — 5 mo. 3. Petechiae — 1 wk. 4. Vomiting — 1 wk. 5. Bleeding gums — 1 wk.	A. Leukemia April 1940 B. No R	Gen. enlargement (2×)	6	3	1. Ecchymoses 2. Enlarged tonsils	28	15.5		Wass.—neg. Bl. culture—non-hemolytic staph. albus		7/14/40 2 (O.)		7/12/40 to 7/20/40	4	1750
	60 Kin.	M 9	5/16/38	1. Weakness 2. Anorexia 3. Epistaxis 4. Bone pains — 3 mo.	A. Leukemia Mar. 1938 B. 8 transfusions	Gen. enlargement (4×)	5	5	1. Pallor 2. Epistaxis	36	116		Wass.—neg.	R—most bones	5/19/38 to 5/24/38 11.68 (O.)		5/28/38 to 6/ 5/38	5	1320
	61 Iud.	M 23	12/19/40	1. Sore throat 2. Enlarged cervical nodes 3. Sternal pain — 3 wks.	A. Leukemia Nov. 1940 B. 1 X-ray R	Gen. enlargement (2×), tender	1	7		39	400				12/20/40 to 12/24/40 6.99 (O.)	12/27/40 100 r			
	E. 62 Rog.	F 58	9/ 6/40	1. Weakness 2. Abdominal distention 3. Vomiting 4. Indigestion, gas — 1 mo.	A. None B. Abdominal tap (8/25/40); 6 pts. fluid withdrawn	Shotty, firm	2		1. Ascites 2. Edema of thighs	60	625				9/15/40 6.6 (O.)				
	M. 63 Rog.	F 52	3/ 2/40	1. Weakness 2. Profuse perspiration 3. Loose stools — 1 yr. 4. Ascites—6 mo.	A. None B. No R	Gen. enlargement (2×)	6	2.5	1. Ascites	58	125		Cell culture—blood lymphocytes grew readily		3/ 4/40 to 4/ 5/40 17.33 (O.)				
	* K. 64 Smi.	F 24													12/14/37 to 2/24/38 44.0 (O.)				
	65 Tui.	F 27	7/23/40	1. Tiredness—1 yr. 2. Pallor, dyspnea — 3 mo. 3. Abdominal pain — 3 mo. 4. Petechiae — 1 wk. 5. Bleeding gums — 1 wk.	A. None B. No R	Gen. enlargement (1×), tender	4 tender	2	1. Petechiae 2. Spine tender 3. Ecchymoses	66	104		Wass.—neg. Feces—pos. Occult bl.	R—most bones	7/25/40 4.0 (O.)		8/ 1/40 to 8/12/40	5	2050
	66 Wel.	M 30	6/ 6/40	1. Swelling of lymph nodes 2. Dyspnea 3. Loss of weight — 3 mo.	A. None B. No R	Gen. enlargement (4×)	5		1. Petechiae 2. Hemorrhage in conjunctiva 3. Enlarged tonsils	33	112				6/25/40 to 6/28/40 9.1 (O.)	6/25/40 to 7/ 1/40 3000 r	6/13/40 to 6/25/40	3	1500

* Published previously.

TABLE III (*Continued*)

Chronic

Clinical Data Previous to Administration of Radio-Phosphorus														Treatment				
					Physical and Lab. Findings on Admis.						Biopsy			P^{32}	Radiation	Transfusion		
Name and Number	Sex and Age in Years	Date of Admission	Chief Complaints and Duration of Chief Complaints on Admission	A. Diagnosis and B. Treatment Previous to Admission	Characteristics of Peripheral Lymph Nodes	Extension of Spleen Below Costal Margin in Cm.	Extension of Liver Below Costal Margin in Cm.	Other Findings	Hb (%) Sahli	WBC/Cu. Mm. in Thous.	M = Sternal Marrow L = Lymph Node R = Rib Marrow S = Skin Hyper = Hyperplastic	Chemistry and Serology, etc.	Roentgenological Findings O = Osteoporosis R = Rarefaction	Dates and Total Dosages of Radio-Phosphorus (in Millicuries) Administered O. = Orally I.V. = Intravenously	X-Radiation or Neutron Radiation and Dates	Dates	Number	Total Amount of Blood in c.c.
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
67 Abn.	M 73	8/19/40	1. Leg cramps 2. Dizziness 3. Weakness—8 mo. 4. Dyspnea—6 mo. } 3 wks.	A. None B. No R	Gen. enlargement (2×)	3	2	1. Bilateral hernia 2. Pitting edema of legs	35	273	M—hyper. (lymphocytes predominate)	Blood urea—25 mg. per 100 c.c. of blood		8/21/40 5.0 (O.)				
68 Bean.	M 51	9/23/40	1. Gen. enlargement of nodes—appeared first in 1932	A. Leukemia B. Much X-radiation from 1932 on	Cervical (4×), others (2×)	4	1		29	3	L—leukemic infiltration			9/23/40 5.1 (O.)		9/12/40 to 9/27/40	28	14000
69 Cal.	M 73	8/ 2/39	1. Weakness 2. Anorexia 3. Fever 4. Loss of weight } 6 mo.	A. Leukemia 1935 B. X-radiation (5000 r)	Gen. enlargement	1	2	1. Mastoiditis (right)	64	19				8/38 6.01 (O.) 5/39 13.32 (O.)		8/ 2/39 to 9/24/39	4	2000
70 Chi.	M 69	1/13/40	1. Weakness 2. Difficulty in walking } 6 mo.	A. Leukemia May, 1936 B. X-radiation	Gen. enlargement (1×)	1		1. Partial paralysis of both legs	100	108	M—hyper. (95% lymphocytes, 5% normoblasts)			1/13/40 13.6 (O.) 3/24/40 15.0 (O.)				
71 Dry.	M 55	5/11/40	1. Fatigue 2. Weakness 3. Cough } 11 yrs.	A. Leukemia May 1929 B. X-radiation and Fowler's solution	Shotty	2	1		94	195				5/11/40 to 1/ 2/41 1.36 (I.V.) 21.2 (O.)				

TABLE III (*Continued*)

Chronic	72 Foo.	F 50	8/30/40	1. Weakness 2. Pallor 3. Enlargement of abdomen and of nodes — 1 yr.	A. Lymphoid leukemia Jan. 1940 B. No R	Gen. enlargement (3×)	20	2		40	96				8/30/40 to 2/ 5/41 25.0 (O.)				
	73 Fra.	F 70	4/16/40	1. Weakness—3 yrs.	A. Leukemia Mar. 1937 B. X-radiation	Gen. enlargement (3×)	5	5		61	1000				4/23/40 1.5 (I.V.) 4/24/40 4.7 (O.)				
	74 Gra.	F 47	4/23/40	1. Weakness 2. Bruises easily — 3 yrs.	A. Leukemia Jan. 1937 B. Fowler's solution	Gen. enlargement (2×)				97	104				4/29/40 to 1/22/41 4.5 (I.V.) 22.74 (O.)				
	75 Hat.	M 72	2/20/40	1. Weakness 2. Anorexia 3. Purpura — 6 yrs.	A. Leukemia 1934 B. Fowler's solution, benzol, X-radiation	Gen. enlargement (1×)			1. Purpura on scrotum and thighs	97	110	M—hyper. (81% lymphocytes)			2/21/40 to 3/18/41 59.75 (O.)				
	76 Hog.	M 66	7/ 6/39	1. Weakness 2. Enlarged abdomen 3. Swollen ankles 4. Bone aches — 6 mo.	A. Leukemia Jan. 1939 B. No R	Gen. enlargement (3×)	9		1. Heart enlarged 2. Leukemids of hands, feet, and abdomen	62	223		Wass.—neg.		8/18/39 to 1/ 3/41 4.8 (I.V.) 20.12 (O.)	7/24/40 50 r Spleen			
	77 Lea.	F 61	11/ 8/40	1. Weakness 2. Anorexia 3. Loss of weight 4. Diaphoresis — 9 mo.	A. Leukemia Sept. 1940 B. No R	Gen. enlargement (2×)	20	18	1. Gen. purpura	62	403		Wass.—neg.		11/16/40 2.6 (I.V.) 12/15/40 2.6 (I.V.)				
	78 Lyt.	M 59	3/18/40	1. Weakness—1 yr. 2. Enlargement of lymph nodes — 6 mo.	A. Leukemia Nov. 1939 B. Fowler's solution	Gen. enlargement (2×)				107	43		Wass.—neg.		3/23/40 to 9/27/40 23.0 (O.)				
	79 Mil.	F 61	9/30/40	1. Weakness 2. Abdominal pain — 4 mo.	A. Lymphoid leukemia Sept. 1940 B. No R	Gen. enlargement (2×)	16	2	1. Purpura on both lower extremities	44	114				9/30/40 to 12/27/40 28.35 (O.)				
	80 Mic.	M 55	10/25/38	1. Weakness 2. Cough 3. Enlarged abdomen — 4 wks. 4. Swollen ankles—1 wk.	A. Leukemia July 1938 B. X-radiation	Gen. enlargement (2×)	7	5	1. Pallor	44	423	M—hyper. (90% lymphocytes) L—lymphoid hyper.	Wass.—neg.		2/ 9/39 to 3/ 9/40 59.42 (O.)	2/ 9/39 120 r (Heublein)	2/ 9/39	1	500

TABLE III (*Continued*)

Clinical Data Previous to Administration of Radio-Phosphorus

Treatment

	Name and Number	Sex and Age in Years	Date of Admission	Chief Complaints and Duration of Chief Complaints on Admission	A. Diagnosis and B. Treatment Previous to Admission	Physical and Lab. Findings on Admis.: Characteristics of Peripheral Lymph Nodes	Extension of Spleen Below Costal Margin in Cm.	Extension of Liver Below Costal Margin in Cm.	Other Findings	Hb (%) Sahli	WBC/Cu. Mm. in Thous.	Biopsy: M = Sternal Marrow, L = Lymph Node, R = Rib Marrow, S = Skin, Hyper = Hyperplastic	Chemistry and Serology, etc.	Roentgenological Findings: R = Rarefaction	P^{32}: Dates and Total Dosages of Radio-Phosphorus (in Millicuries) Administered; O. = Orally, I.V. = Intravenously	Radiation: X-Radiation or Neutron Radiation and Dates	Transfusions: Dates	Transfusions: Number	Transfusions: Total Amount of Blood in c.c.
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Chronic	81 Por.	M 64	9/20/40	1. Weakness—14 mo. 2. Nausea 3. Headache } 2 wks. 4. Loss of weight	A. Leukemia June 1939 B. Liver extract	Shotty, firm	6	3		69	126	M—hyper. (94% lymphocytes)			9/23/40 to 2/ 1/41 9.0 (O.) 4.5 (I.V.)				
	82 Sad.	M 48	1/18/41	1. Gradual paralysis of legs over a three-year period	A. Leukemia Apr. 1938 B. No R	Gen. enlargement (2×)	2	3	1. Spastic paralysis of both legs necessitating use of two canes	116	54	M—hyper. (infiltrated with lymphocytes)			1/17/41 5.0 (O.) 1/28/41 5.0 (I.V.)				
	83 San.	M 59	12/28/39	1. Weakness—1 yr. 2. Slimy stools—9 mo. 3. Headache—2 mo.	A. None B. No R	Gen. enlargement (2×)	4	3	1. Pallor	43	21	M—hyper. (30% lymphocytes)	Wass.—neg. Gastric juice—no free HCl		12/31/39 to 8/19/40 33.63 (O.)				
	84 Sap.	M 50	1/17/40	1. Weakness 2. Marked enlargement of cervical glands } 3 yrs. 3. Slimy stools	A. Leukemia Mar. 1938 B. X-radiation	Enlarged cervical nodes (8×), others (2×)	4	1		98	53				1/20/40 to 4/30/40 41.7 (O.)				
	85 Shi.	M 54	7/ 5/38	1. Weakness 2. Enlarged nodes 3. Enlarged abdomen } 11 mo.	A. Leukemia July 1938 B. X-radiation (6000 r)	Ax. nodes (6×), others (2×)	8	2		78	92	L—lymphoid infiltration	Spinal puncture—lymphocytes, 500 per cu. mm.		12/ 7/39 to 1/18/40 20.45 (O.)				

TABLE III (*Continued*)

Chronic	86 Sch.	M 54	8/16/40	1. Weakness 2. Headache 3. Enlarged inguinal glands — 1 wk.	A. Leukemia Sept. 1940 B. Fowler's solution, transfusions	Gen. enlargement (2×)	2	2	1. Superficial abdominal veins distended	37	197	L—lymphoid infiltration			10/20/40 20.0 (O.)		10/21/40 to 11/ 6/40	6	2350
	87 Tay.	M 49	11/ 2/39	1. Weakness 2. Mucoid stools 3. Sleepiness — 6 mo.	A. None B. No R	Gen. enlargement (2×)	6		1. Pallor	72	325	L—lymphoid infiltration	Wass.—neg.		11/ 9/39 to 3/ 7/40 25.33 (O.)				
	88 Tod.	M 45	11/14/40	1. Occasional weakness — 1 yr.	A. Leukemia Oct. 1939 B. X-radiation	Gen. enlargement (1×)	1	2	1. Occasional toothache	110	70	M—hyper. (lymphoid cells predominate)				11/29/40 to 1/31/41 50 n			
	89 Val.	M 66	1/25/40	1. Gen. lymphadenopathy — 1 yr. 2. Weakness—1 mo.	A. None B. No R	Gen. enlargement (2×)	2	2		70	87		Wass.—++++		1/14/40 to 2/ 3/40 9.3 (O.)				
	90 Vol.	F 74	3/ 9/39	1. Enlarged abdomen 2. Enlarged peripheral lymph nodes — 1 yr.	A. None B. No R	Gen. enlargement (2×)	8	2	1. Ascites 2. Edema of ankles	42	119		Wass.—neg.		3/17/39 to 4/ 6/39 12.24 (O.)		3/17/39 to 4/ 6/39	2	1000
	91 You.	M 67	4/11/40	1. Enlarged glands — 10 mo. 2. Fatigue—3 mo.	A. Leukemia Jan. 1940 B. X-radiation (3360 r)	All nodes 1 cm. in diam.	6			95	66	M—hyper. (48% lymphocytes)			4/12/40 2.16 (I.V.) 4/23/40 to 1/20/41 24.0 (O.)				

TABLE III (*Continued*)

Clinical Data After Administration of Radio-Phosphorus

	Name and Number	Sex and Age in Years	Date of Admission	Physical and Lab. Findings: LN = Lymph Node; S = Spleen; L = Liver; I = Increased; D = Decreased; U = Unchanged; Refers to Change in Size After That Found on Admission	Min. and Max. Levels: Hb (%) Sahli	Min. and Max. Levels: WBC/Cu. Mm. in Thous.	Remissions: Partial — Patient Essentially Normal Clinically. Associated with a Distinct Improvement in Hb and WBC Levels for Periods of A = 3 Mos., B = 6 Mos., C = 1 Yr.	Remissions: Complete — Patient Clinically and Hematologically Normal for Periods of A = 3 Mos., B = 6 Mos., C = 1 Yr.	General Condition of Patient as of March 15, 1941	Date of Death	Hours Between Death and Autopsy	Postmortem Findings: Gross Findings (Weights in Grams)	Postmortem Findings: Microscopical Findings	Radio-Phosphorus Studies: Peripheral Blood = P.B. Excretions = E. Tissue = T.	Number
	1	2	3	20	21	22	23	24	25	26	27	28	29	30	31
Acute	51 Ande.	F 4	1/27/41	LN—D S—D L—U	87 to 66	1750 to 4100				Type 14 Pneumonia 2/28/41	3	Left lung—295 Rt. lung—150 Liver—1100, spleen—80 Consolidation of left lung		T.	51
	52 Andr.	F 1½	9/11/40	LN—U S—U L—U						9/17/40	6	Typical findings	Marrow—typ. leukemic hyperplasia. Liver—fatty degeneration. Kidneys—marked infiltration. Nodes and spleen—leuk. infiltration	T.	52
	53 Bel.	M 37	7/15/39	LN—I S—I L—U	21 to 64	21 to 125				9/ 1/39	6	Liver—2350, spleen—800, kidneys—firm	Lymphoid infiltration of most organs, including marrow, kidneys, and submucosa of G.I. tract	T.	53
	54 Bor.	M 2	4/ 5/39	LN—I S—U L—D	25 to 70	4 to 20				7/22/39	4	Liver—560, spleen—100	Lymphoid infiltration of most organs, including marrow, kidneys, and submucosa of G.I. tract		54
	55 Bri.	F 8	12/10/40	LN—U S—U L—U	Unchanged	Unchanged				1/ 3/41	6	Typical findings	Lymphoid infiltration of many tissues (bone, G.I. tract, kidneys, marrow, spleen)	P.B. E. T.	55
	56 Cre.	F 3	11/25/40	LN—D (Normal) S—D (Not palp.) L—D (Not palp.)	100	5000		2 mo.	Excellent						56
	57 Fie.	M 8	11/23/40	LN—U S—U L—U	80	6	2 mo.			2/25/41					57
	58 Gre.	M 45	4/17/40	LN—U S—U L—U	32 to 50	8 to 28				5/19/40	6	Hepato-splenomegaly and lymphadenopathy. Marrow red		T.	58

TABLE III (*Continued*)

TABLE III (*Continued*)

Acute	59 Her.	M 4	7/12/40	LN—U S—U L—U	28 to 35	1 to 15				7/24/40				P.B. T.	59
	60 Kin.	M 9	5/16/38	LN—D S—D (1 cm.) L—D (1 cm.)	36 to 80	1 to 116				6/12/38					60
	61 Iud.	M 23	12/19/40	LN—U S—U L—U						12/28/40				P.B. E.	61
	E. 62 Rog.	F 58	9/ 6/40	LN—U S—U L—U	No change	No change				9/17/40	7	Spleen—1600, liver—2400. G.I. tract markedly infiltrated with perforation of duodenum	Marrow—hyperplastic (lymphoid infiltration). Kidneys and G.I. tract markedly infiltrated	T.	62
	M. 63 Rog.	F 52	3/ 2/40	LN—U S—D (2 cm.) L—D (1 cm.) (ascites disappear)	28 to 45	2 to 110				5/27/40				P.B. T.	63
	* K. 64 Smi.	F 24								2/26/38	18	Spleen—300, liver—1800. All nodes and marrow uniformly gray	Liver, kidneys, spleen, lungs, nodes and marrow diffusely infiltrated with lymphoid cells	T.	64
	65 Tui.	F 27	7/23/40	LN—U S—U L—U	23 to 66	1 to 104				8/13/40				T.	65
↓	66 Wel.	M 30	6/ 6/40	LN—I S—I L—I	20 to 33	100 to 119				7/ 5/40	8	Spleen—900, liver—1850. Both peripheral and central nodes markedly enlarged	Leukemic infiltration of kidneys, heart, liver, submucosa of G.I. tract, lung, and hematopoietic system	T.	66
↑	67 Abn.	M 73	8/19/40	LN—U S—U L—U	20 to 35	75 to 426				11/28/40	6	Broncho-pneumonia. Early fibrosis of liver. Myocardial sclerosis and degeneration. Pul. edema	Typical leukemic infiltration	P.B.	67
Chronic	68 Bean.	M 51	9/23/40	LN—U S—U L—U	No change	No change				9/29/40	6	Spleen—2200, liver—1800. Pancreas unusually hard. Marrow pale and watery	Lymphocytic infiltration of marrow, G.I. tract, kidneys, spleen, pancreas	T.	68
	69 Cal.	M 73	8/ 2/39	LN—U S—U L—U	64 to 79	19 to 23				9/30/39	–				69
	70 Chi.	M 69	1/13/40	LN—U S—U L—U	60 to 77	6 to 131				5/29/40	7 days	Liver—1700, spleen, kidneys—150. Marrow red and mushy		T.	70
	71 Dry.	M 55	5/11/40	LN—D S—D L—D	94 to 114	20 to 195	B		Excellent					P.B. E.	71

TABLE III (*Continued*)

Clinical Data After Administration of Radio-Phosphorus

	Name and Number	Sex and Age in Years	Date of Admission	Physical and Lab. Findings: LN = Lymph Node; S = Spleen; L = Liver; I = Increased; D = Decreased; U = Unchanged; Refers to Change in Size After That Found on Admission	Min. and Max. Levels: Hb (%) Sahli	Min. and Max. Levels: WBC/Cu. Mm. in Thous.	Remissions: Partial — Patient Essentially Normal Clinically. Associated with a Distinct Improvement in Hb and WBC Levels for Periods of A = 3 Mos., C = 1 Yr.	Remissions: Complete — Patient Clinically and Hematologically Normal for Periods of A = 3 Mos., B = 6 Mos., C = 1 Yr.	General Condition of Patient as of March 15, 1941	Date of Death	Hours Between Death and Autopsy	Postmortem Findings: Gross Findings (Weights in Grams)	Postmortem Findings: Microscopical Findings	Radio-Phosphorus Studies: Peripheral Blood = P.B. Excretions = E. Tissue = T.	Number
	1	2	3	20	21	22	23	24	25	26	27	28	29	30	31
Chronic	72 Foo.	F 50	8/30/40	LN—D S—D (15 cm.) L—D (1 cm.)	54 to 65	51 to 95			Good						72
	73 Fra.	F 70	4/16/40	LN—U S—U L—U	49 to 61	1000 to 1000				6/22/40				P.B.	73
	74 Gra.	F 47	4/23/40	LN—D S—U L—U	78 to 104	27 to 117	B		Excel-lent					P.B. E.	74
	75 Hat.	M 72	2/20/40	LN—U S—U L—U	62 to 97	18 to 120	C		Good					P.B.	75
	76 Hog.	M 66	7/ 6/39	LN—D (1 cm.) S—D (3 cm.) L—U	47 to 109	8 to 223	C		Good						76
	77 Lea.	F 61	11/ 8/40	LN—U S—D (8 cm.) L—D (6 cm.)	58 to 62	441 to 229				12/24/40	9	Spleen—900, liver—2500. Mesenteric nodes were massive. Broncho-pneumonia	Typical gen. lymphocytic infiltration	P.B. T.	77
	78 Lyt.	M 59	3/18/40	LN—U S—U L—U	96 to 107	19 to 74			Excel-lent					P.B.	78
	79 Mil.	F 61	9/30/40	LN—U S—U L—U	23 to 44	70 to 376				12/27/40					79

TABLE III (*Continued*)

			S—U L—U	23 to 44	70 to 376			12/27/40						79

TABLE III (*Continued*)

Chronic

80 Mic.	M 55	10/25/38	LN— S— L—	44 to 71	11 to 423	A 2 occasions								80
81 Por.	M 64	9/20/40	LN—D S—D (2 cm.) L—D (1 cm.)	69 to 90	10 to 70			Good					P.B.	81
82 Sad.	M 48	1/18/41	LN—D S—D (1 cm.) L—D (1 cm.)	87 to 116	10 to 52			Walking has improved					P.B. E.	82
83 San.	M 59	12/28/39	LN—U (not palp.) S—D (not palp.) L—D (not palp.)	43 to 88	6 to 21		C	Excellent						83
84 Sap.	M 50	1/17/40	LN—D S—D (1 cm.) L—U	43 to 81	46 to 78				5/ 6/40	12	Liver—175, spleen—500. Small white nodules seen in liver and spleen	Small tumor masses and necrotic areas in spleen and liver. Lymphoid infiltration of submucosa of G.I. tract, liver, and kidneys	P.B. T.	84
85 Shi.	M 54	7/ 5/38	LN—D (2 cm.) S—D (1 cm.) L—D (1 cm.)	62 to 78	15 to 92				8/ 7/40	6	Pneumonia—type 7. Lymphocytic meningeal infiltration. Pulmonary edema	Lymphoid infiltration of all organs, including eyes, brain, kidneys and G.I. tract	T.	85
86 Sch.	M 54	8/16/40	LN—U S—U L—U	23 to 41	41 to 200				11/ 8/40	48	Liver—2400, spleen—1100. Enlargement of all lymph nodes. Papilloma of stomach mucosa near pylorus	Typical leukemic infiltration of all organs, including kidneys and G.I. tract	P.B. T.	86
87 Tay.	M 49	11/ 2/39	LN—D S—D (2 cm.) L—U	45 to 62	13 to 300	A			5/11/40	1½	Liver—2100, spleen—610, kidneys—200. Diffuse diverticulosis with diverticulitis following perforation	Lymphoid infiltration of most organs, esp. marrow, lymph nodes, submucosa of G.I. tract. Diverticulitis. Coli bacillus septicemia		87
88 Tod.	M 45	11/14/40	LN—D S—D (not palp.) L—D (not palp.)	110 to 120	17 to 75	A		Excellent						
89 Val.	M 66	1/25/40	LN—U S—U L—U	70 to 80	10 to 87				2/22/40					89
90 Vol.	F 74	3/ 9/39	LN—U S—D L—U (ascites disappear)	28 to 42	6 to 119				5/22/39	2	Ascites—4000 c.c., liver—1820, spleen—2040. Mesentery was a solid mass of lymphoid tissue	Lymphoid infiltration of all organs, particularly submucosa of G.I. tract and bone marrow	T.	90
91 You.	M 67	4/11/40	LN—D S—D L—U	60 to 99	28 to 94	B		Good					P.B. E.	91

In the study of the patients treated with radio-phosphorus, standardized technic for diagnosis was used. All blood used for cell counts was obtained from puncture wounds of the lobe of the ear. Sahli and Sahli-Osgood hemoglobinometers, and standardized blood cell pipettes were used. Most of the differential cell counts of the blood and of the bone marrow fluid, obtained by sternal puncture, were made by use of the supra-vital technic as well as by the usual Wright Giemsa staining technic. The blood (the amount of which depended on the white cell count, but usually varied from 15 to 50 c.c.) used for radioactivity assays was withdrawn from veins, heparinized, immediately cooled and centrifuged in cold centrifuge cups for 20 minutes at 3000 revolutions, or 1450 times gravity (International Centrifuge, Size 2). First, the buffy coat was removed with a 10 c.c. syringe and a 4-inch 18-gauge needle, the bevelled point of which had been ground off. By gently loosing and aspirating one edge of the buffy coat under good light, the entire coat (which has internal tenacity) along with considerable plasma can be removed from the initial site of aspiration without disturbing the layer of red blood cells or leaving a suspension of cells in the plasma. After the buffy coat, or white cell layer, had been removed, the plasma layer was aspirated off. Equal quantities of isotonic Ringer's solution were then added to both of the suspensions of red blood cells and white blood cells. Both the white and the red cells were gently shaken to wash off the clinging plasma and then the suspensions were centrifuged exactly 20 minutes at 1,450 times gravity so that constant volumes were obtained. Accurate volumetric readings of these packed cells were possible.

Fractions of blood, and aliquot portions of feces and urine were placed in appropriate crucibles and ashed (at 400° C.) The radioactivity of each ash was measured by means of DuBridge electrometers, Lauritsen type electroscopes or Geiger counters, each of which was standardized by a uranium standard which is known to emit 500 beta-particles per second. The figures representing the radioactivities were corrected for the rate of decay of radio-phosphorus as indicated on the accompanying tables and graphs.

Results *

A. Introductory Remarks on Absorption and Excretion of Radio-Phosphorus.

The absorption of orally administered radio-phosphorus from the contents of the gastrointestinal tract depends upon numerous factors,[37] among which the important ones are the speed of the phosphorylating mechanism within the gastrointestinal tract and within the body tissues themselves; the metabolic rate, the blood volume, the diet, the age and weight of the patient;

* It must be pointed out again that all the cases on whom absorption and excretion studies were made received "therapeutic" and not "tracer" doses of radio-phosphorus. Therefore exact conclusions concerning the metabolism of phosphorus in leukemia cannot be drawn. Similarly, the doses of phosphorus used in the normal cases may well have produced irradiation effects. However, no changes of the levels of the white blood cells or other evidences of such irradiation effects were observed in the normal individuals.

the intake of P^{31} present in the diet; the amount of sodium phosphate ingested in which the radio-phosphorus is incorporated; the rate of the fecal flow and the vascularity of the gastrointestinal tract; the rates of phosphorus metabolism and the functional capacity of each organ and tissue. Not all of these factors are involved when P^{32} is administered intravenously. Obviously the disease processes to be studied and their effects upon the organs of the body are additional complicating factors. In order to study accurately the phosphorus metabolism of the body, all the factors mentioned and many more would have to be controlled or measured. The effect of one of these factors on absorption was noted. In table 7 (Case 34) it is observed that when large amounts of non-radioactive phosphorus accompany radio-phosphorus, regardless of the method of administration, less of the radio-phosphorus is retained by the blood fractions. This indicates that the varying intake of P^{31} in the average diet will have some effect on the rate of the absorption of administered radio-phosphorus.

The average normal adult person has about 5,000 c.c. of circulating blood, the proportions of which are roughly as follows: 2,250 c.c. red blood cells, 50 c.c. white blood cells, and 2,700 c.c. plasma. Patients with leukemia may have fewer than 50 c.c. or as much as 3,000 c.c. of circulating white blood cells, or they may have fewer than 1,000 c.c. of circulating red blood cells but they rarely have more than 2,500 c.c. Therefore, it must be pointed out that the results have been illustrated on figure 1 as per cent of the dose of radio-phosphorus administered per 100 c.c. of plasma, whole blood, packed red blood cells, or packed white blood cells. It must be emphasized that figure 1 and figure 2 illustrate only trends. The data for drawing the curves were obtained from tables 7, 8 and 9. Obviously, there are many variations, such as differences in the weights of the patients, differences in the amounts of P^{32} and P^{31} administered, differences in the volumes of the circulating blood elements, differences in the metabolic rates of the blood elements, and others for which corrections were not made.

The rate of excretion of radio-phosphorus in the urine and feces depends upon all the factors mentioned previously and particularly upon the route of administration of P^{32}. The rate of flow of the fecal stream, the total amount of P^{31} and the absorptive capacities and the vascularity of the intestinal mucosa, are among the factors influencing the rate of excretion in the feces when P^{32} is administered orally. When administered orally, P^{32} may or may not be absorbed; if absorbed, may or may not be excreted by the kidneys; or may or may not be excreted by the bowel. When administered intravenously P^{32} can only reach the feces by way of the biliary system or by direct excretion through the gastrointestinal mucosa. (One nervous patient, case 71, who had received intravenously 2.16 Mc of P^{32}, vomited four hours after the administration, and 0.06 per cent of the dose was found in 40 c.c. of vomitus.) The rate of excretion of P^{32} in the urine depends upon the amount of P^{32} available in the plasma and upon kidney function. The results have been illustrated in figure 2 as percentage of the dose administered.

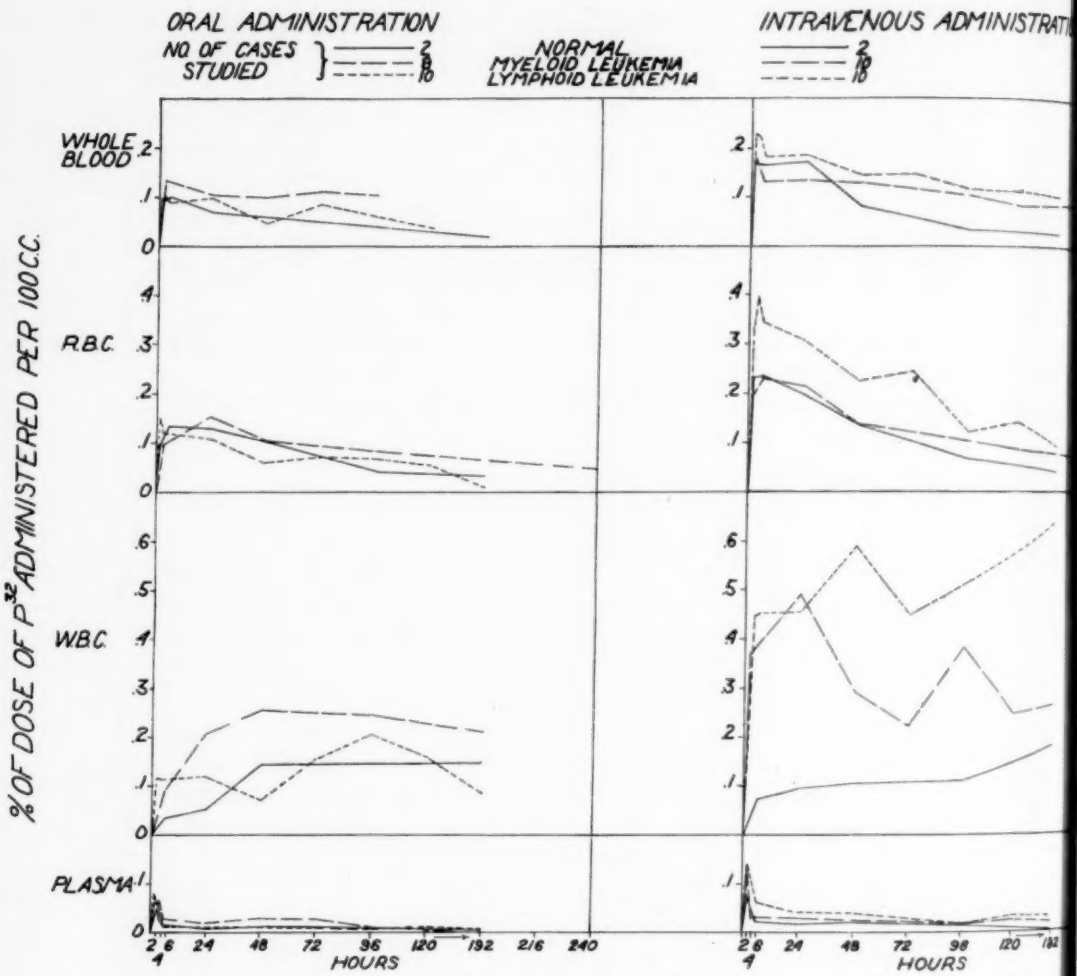

FIG. 1. Average retention, in blood fractions, of P^{32} administered orally and intravenously in normal individuals and in patients with leukemia.

B. Oral Administration of Radio-Phosphorus.

1. Absorption (tables 7 and 8 and figure 1, left side).

The rate of absorption of radioactive phosphorus administered orally has been measured in two normal persons and in 18 patients (2 acute and 16 chronic cases). The content of radio-phosphorus in the plasma of all the patients and of the normal persons was greatest before the second hour after administration. After the twenty-fourth hour, lower levels were observed which gradually tapered off to the near zero level on the eighth day.

The maximum level of radio-phosphorus in the red blood cells usually occurred between the sixth and twenty-fourth hours after administration. No correlation could be established between the concentration of radio-phosphorus and the degree of anemia or the amount of hemoglobin.

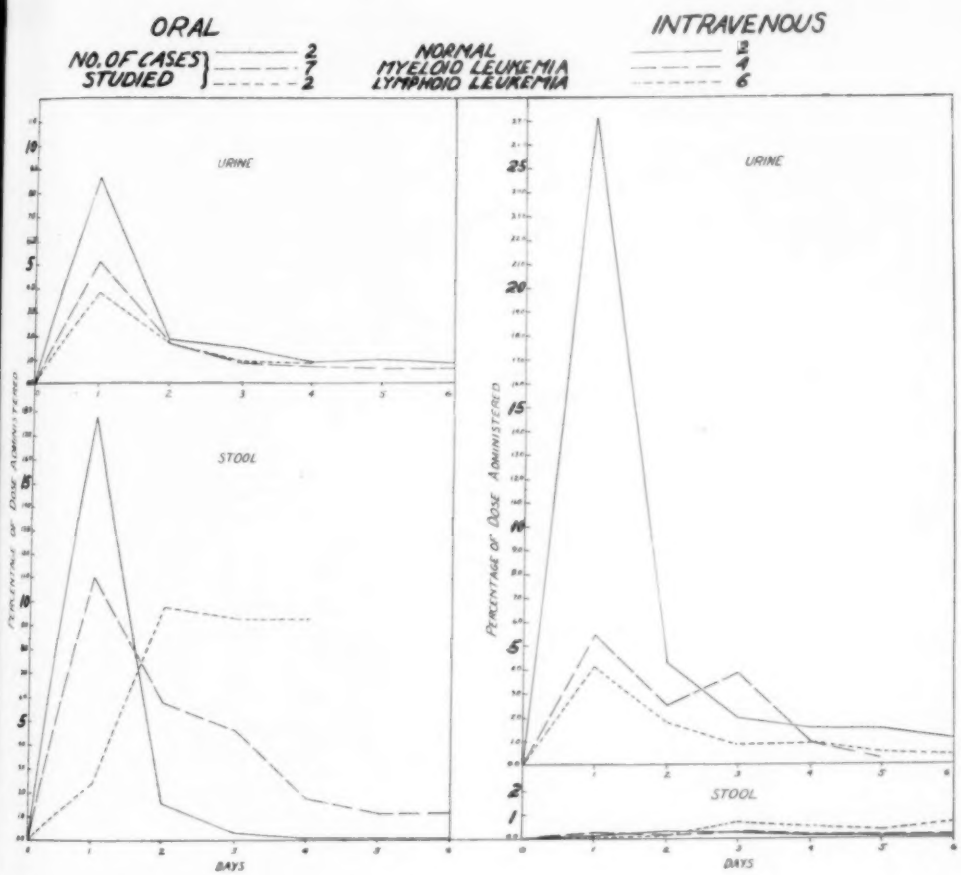

FIG. 2. Average excretion of P^{32} in urine and feces.

In the majority of cases, regardless of the chronicity or acuteness of the leukemic process, the P^{32} levels of the white blood cells rose during the first 48 hours and then either continued to rise slowly or maintained a high plateau for days. The content of radio-phosphorus in the white blood cells of normal persons was considerably lower during the first 48 hours than that of leukemic patients, i.e. normal white blood cells retain less radio-phosphorus than leukemic cells. This may be due, among other reasons, to a more rapid rate of phosphorus metabolism, or a more rapid rate of reproduction of the leukemic cells. Unfortunately, the metabolic rates of the leukemic cells were not determined.[15]

In case 97 it was possible to measure the amount of radio-phosphorus retained by the platelets. Twenty-four hours after administration, the platelets retained the same amount of radio-phosphorus per unit volume as did the red blood cells.

TABLE VII

Rates of Absorption (Retention) of Radio-Phosphorus in Blood

	Periods after Oral Administration of P^{32}																Time (Days) for Values Under "Other" ←	Milligrams of Sodium Phosphate in Which P^{32} Was Incorporated	Micro-curies of P^{32} Administered Orally	Name and No. of Pts. Receiving Radio-Phosphorus Orally
	2 Hours		4 Hours		6 Hours		24 Hours		48 Hours		72 Hours		96 Hours		Other					
	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%				
I. Normal Individuals																				
Whole blood	.0091	.0606			.0102	.068	.0071	.0473	.0060	.0400			.0037	.0246	.0015	.0100				
R.B.C.	.0080	.0533			.0131	.0873	.0137	.0913	.0970	.6465			.0048	.0320	.0041	.0273	8	600	1500	Mie 1
W.B.C.	.0087	.0580			.0013	.0086	.0040	.0266	.0050	.0332			.0104	.0693	.0090	.0600				
Plasma	.0092	.0613			.0024	.0160	.0016	.0106	.0017	.0113			.0015	.0100	.0005	.0033				
Whole blood	.0192	.1280			.0206	.1373	.0150	.1000	.0128	.0853			.0089	.0593	.0045	.0300				
R.B.C.	.0215	.1433			.0263	.1753	.0249	.1660	.0170	.1133			.0080	.0533	.0049	.0326	8	600	1500	Rob 3
W.B.C.	.0104	.0693			.0030	.0600	.0131	.0873	.0369	.2460			.0319	.2126	.0340	.2266				
Plasma	.0123	.0820			.0039	.0260	.0032	.0215	.0032	.0215			.0032	.0215	.0019	.0126				
II. Myeloid Leukemia																				
Whole blood							.0130	.1530	.0128	.1510			.0108	.1270						
R.B.C.							.0173	.2030	.0132	.1500			.0124	.1460				50	850	Flag 20
W.B.C.							.0427	.5020	.0426	.5020			.0384	.4520						
Plasma							.0030	.0353	.0054	.0640			.0025	.0290						
Whole blood							.0214	.0910	.0196	.0840			.0161	.0690						
R.B.C.							.0291	.1240	.0259	.1100			.0212	.0900				150	2350	Mas 34
W.B.C.							.0398	.1690	.0602	.2560			.0570	.2420						
Plasma							.0061	.0270	.0060	.0260			.0047	.0200						
Whole blood							.0193	.0820	.0153	.0650			.0132	.0560						
R.B.C.							.0252	.1070	.0180	.0770			.0149	.0640				2000	2350	Mas 34
W.B.C.							.0319	.1360	.0378	.1610			.0436	.1860						

TABLE VII (*Continued*)

Plasma							.0036	.0150	.0037	.0160			.0028	.0120				2000	2350	Mas 34

R.B.C.							.0252	.1070	.0180	.0770			.0149	.0640					
W.B.C.							.0319	.1360	.0378	.1610			.0436	.1860			2000	2350	Mas 34

TABLE VII (*Continued*)

Plasma							.0036	.0150	.0037	.0160			.0028	.0120					
Whole blood															—				
R.B.C.															.091	.0722			
W.B.C.															.2360	.1870	6	20	12600
Plasma															.0190	.0151			
Whole blood									—				—		—				
R.B.C.									.0410	.0873			.0290	.0618	.0010	.0213			
W.B.C.									.0680	.1450			.0620	.1320	.0620	.1320	14	3000	4700
Plasma									.0060	.0128			.0020	.0044	.0020	.0043			
							.0630 (Plate	.1050 lets)											
R.B.C.	.0173	.0290	.0320	.0540	.0480	.0800	.0685	.1150							.0254	.0420			
W.B.C.	.0125	.0210	.0210	.0350	.0344	.0570	.0335	.0560							.0800	.1340	10	2800	5960
Plasma	.0188	.031	.0216	.0360	.0184	.0310	.0058	.0090							.0038	.0060			
Whole blood																			
R.B.C.							.0130	.2200	.0510	.1100			.0280	.0650	.0180	.0490			
W.B.C.							.0940	.2000	.1030	.2300			.1360	.2300	.1400	.3000	9	1250	4700
Plasma							.0090	.0230	.0020	.0210			.0040	.0150	.0040	.0010			
Whole blood			.0130	.1310							.011	.1160							
R.B.C.			.0140	.1430							.015	.1500							
W.B.C.			.0220	.2240							.047	.473						830	1000
Plasma			.0100	.1020							.0020	.026							
Whole blood					—		—												
R.B.C.					.0470	.0670	.0976	.1370											
W.B.C.					.0900	.1270	.1390	.2000										2400	7200
Plasma					.0169	.0240	.0129	.0180											
Whole blood																			
R.B.C.																			
W.B.C.																			
Plasma																			

That	45		
Ebey	19		
Hayd	97		
Kenn	27		
Marsh	33		
Rice (Acute Leukemia)	10		

Activities Corrected for Decay and to Date of Administration.

TABLE VII (*Continued*)

	Name and Number of Patients Receiving P^{32} Both Orally and Intravenously	Interval in Days Between Oral and Intravenous Administrations; or I.V. and I.V. Administrations	Name and No. of Pts. Receiving P^{32} Intravenously	Microcuries of P^{32} Administered Intravenously	Milligrams of Sodium Phosphate in Which P^{32} Was Incorporated	Periods after Intravenous Administration of P^{32}																			
						2 Hours		4 Hours		6 Hours		24 Hours		48 Hours		72 Hours		96 Hours		Other		Time (Days) for Values Under "Other"	Other	
						Total	%	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%	← →	Total	%
I. Normal Individuals																									
Whole blood						.0251	.1673			.0249	.1660	.0350	.2333	.0120	.0800			.0058	.0386	.0037	.0246			
R.B.C.			Per			.0336	.2240			.0349	.2326	.0315	.2100	.0198	.1320			.0091	.0606	.0047	.0313			
W.B.C.			2	1500	600	.0401	.2673			.0114	.0760	.0171	.1140	.0160	.1070			.0170	.1133	.0340	.2266	8		
Plasma						.0096	.0640			.0038	.0253	.0023	.0153	.0030	.0207			.0019	.0126	.0009	.0060			
Whole blood						.0260	.1733			.0257	.1713	.0168	.1120					.0033	.0220	.0042	.0280			
R.B.C.			Vic			.0340	.2266			.0352	.2346	.0283	.1886					.0117	.0780	.0071	.0473			
W.B.C.			4	1500	600	.0274	.1822			.0110	.0733	.0113	.0753					.0168	.1120	.0200	.1333	8		
Plasma						.0131	.0873			.0028	.0186	.0036	.0240					.0026	.0173	.0013	.0086			
II. Myeloid Leukemia																									
Whole blood												.0142	.1670	.0171	.2010			.0104	.122					
R.B.C.	Flag											.0201	.2370	.0175	.2060			.0089	.1050					
W.B.C.	20	13		850	50							.0314	.3700	.0351	.4130			.0374	.4400					
Plasma												.0032	.0380	.0023	.0271			.0032	.0380					
Whole blood												.0506	.2150	.0435	.1850			.0495	.2110	.0238	.1010		.0220	.0940
R.B.C.	Maš											.0687	.2920	.0480	.2040			.0263	.1120	.0223	.0950	← 9	.0145	.0620
W.B.C.	34	24		2350	300							.0944	.4010	.0990	.4200			.0827	.3520	.0492	.2090	24 →	.0605	.2580
Plasma												.0075	.0320	.0077	.0328			.0057	.0240	.0050	.0210		.0056	.0240
Whole blood												.0268	.1140	.0250	.1060			.01710	.0730	.0180	.0770			
R.B.C.	Mas											.0442	.1880	.0299	.1270			.0215	.0920	.0141	.0600	←		
W.B.C.	34	21		2350	2000							.0532	.2260	.0610	.2600			.0508	.2160	.0762	.3250	9		

TABLE VII (*Continued*)

W.B.C.	34	21		2350	2000								.0532	.2260	.0610	.2690			.0508	.2160	.0762	.3250	← 9		

TABLE VII (*Continued*)

Plasma													.0057	.0240	.0052	.0221			.0051	.0220	.0041	.0170			
Whole blood						.0202	.1770			.0150	.1300	.0133	.1100												
R.B.C.	That	240		1140	150	.0253	.2220			.0300	.2600	.0380	.3300												
W.B.C.	45					.0570	.5000			.0527	.4600	.0556	.4800												
Plasma						.0141	.1240			.0055	.0400	.0030	.0200												
Whole blood														.0081	.1060	.0080	.1050			.0080	.1050				
R.B.C.			Giral											.0087	.1140	.0091	.1190			.0087	.1140	5			
W.B.C.			21	765	100									.0167	.2180	.0198	.2590			.0156	.2040	←			
Plasma		7												.0023	.0300	.0025	.0330			.0030	.0390				
Whole blood														.0043	.0560	.0054	.0710			.0040	.0520				
R.B.C.			Giral											.0034	.0450	.0040	.0520			.00270	.0350	5			
W.B.C.			21	765	3000									.0151	.1970	.0146	.1910			.0124	.1620	←			
Plasma														.0014	.0180	.0009	.0120			.0006	.0080				
Whole blood												.0274	.1370	.0246	.1320					.0147	.0740		.0128	.0640	
R.B.C.			Hayw									.0257	.1290	.0244	.1220					.0181	.0910	5 ←	.0131	.0660	
W.B.C.			23	2000	143							.0810	.4050	.0520	.2600					.0945	.4730	14	.0396	.1980	
Plasma		14										.0063	.0320	.0062	.0310					.0050	.0250	→	.0041	.0210	
Whole blood												.0276	.1380	—						.0199	.1000				
R.B.C.			Hayw									.0440	.2200	.0366	.1830					.0216	.1080	5			
W.B.C.			23	2000	2000							.0815	.4080	.0776	.3880					.0600	.3000	←			
Plasma												.0060	.0300	.0060	.0300					.0060	.0300				
Whole blood								.0193	.0900			.0168	.0800	.0242	.1200			.0076	.0200						
R.B.C.			Klin											.0172	.0800										
W.B.C.			28	1950	300									.0340	.1700										
Plasma								.0068	.0300			.0024	.0100	.0026	.0100			.0019	.0090						
Whole blood						.0202	.1770			.0180	.1400	.0116	.0900					.0103	.0900						
R.B.C.			Park			.0193	.1690			.0275	.2100	.0171	.1300												
W.B.C.			39	1260	150	.0270	.2370			.0270	.2100	.0410	.3200					.0346	.2900						
Plasma						.0163	.1430			.0030	.0200	.0038	.0300					.0020	.0150						

Total Amounts Expressed in Microcuries per c.c.; Percentages in % of Dose per 100 c.c.

TABLE VIII

Rates of Absorption (Retention) of Radio-Phosphorus in Blood

	Periods after Oral Administration of P^{32}																Time (Days) for Values Under "Other"	Milligrams of Sodium Phosphate in Which P^{32} Was Incorporated	Micro-curies of P^{32} Administered Orally	Name and No. of Pts. Receiving Radio-Phosphorus Orally
	2 Hours		4 Hours		6 Hours		24 Hours		48 Hours		72 Hours		96 Hours		Other					
	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%				
I. Normal Individuals																				
Whole blood	.0091	.0606			.0102	.068	.0071	.0473	.008	.04			.0037	.0246	.0015	.010	8	600	1500	Mie 1
R.B.C.	.0080	.0533			.0131	.0873	.0137	.0913	.0097	.0647			.0048	.032	.0041	.0273				
W.B.C.	.0087	.0580			.0013	.0086	.004	.0266	.0050	.0332			.0104	.0693	.009	.06				
Plasma	.0092	.0613			.0024	.016	.0016	.0106	.0017	.0113			.0015	.010	.0005	.0033				
Whole blood	.0192	.1280			.0206	.1373	.0150	.10	.0128	.0853			.0089	.0593	.0045	.030	8	600	1500	Rob 3
R.B.C.	.0215	.1433			.0263	.1753	.0249	.166	.0170	.1133			.008	.0533	.0049	.0326				
W.B.C.	.0104	.0693			.009	.06	.0131	.0873	.0369	.246			.0319	.2126	.034	.227				
Plasma	.0123	.0820			.0039	.026	.0032	.0215	.0032	.0215			.0032	.0215	.0019	.0126				
III. Lymphoid Leukemia																				
Whole blood	.0420	.10	.051	.12			.065	.16										750	4000	Dry 71
R.B.C.	.0399	.09	.072	.17			.102	.25												
W.B.C.	.0643	.16	.089	.22			.151	.37												
Plasma	.051	.12	.0265	.06			.0165	.04												
Whole blood	.0492	.11					.056	.12			.056	.13	.0364	.08				142	4270	Gra 74
R.B.C.	.0496	.11					.0945	.22			.053	.12	.0438	.10						
W.B.C.	.0664	.15					.0946	.22			.162	.38	.1505	.34						
Plasma	.0461	.10					.0159	.03			.007	.01	.0129	.02						
Whole blood							.0453	.0906			.0280	.056			.0186	.037	5	300	5000	Sad 82
R.B.C.							.0268	.0536			.034	.068			.0263	.053				
W.B.C.							.0535	.107			.057	.113			.082	.164				

TABLE VIII (*Continued*)

W.B.C.							.0535	.107			.057	.113			.082	.164	5	300	5000	82

TABLE VIII (*Continued*)

Plasma							.0118	.0236			.0099	.0198			.0081	.016	5	300	5000	Sad 82
Whole blood					.0267	.0535	.0251	.0503	.0232	.0465			.0208	.0416						
R.B.C.					.0553	.111	.0484	.097					.0346	.069				750	5000	Abne
W.B.C.					.0646	.0128	.0419	.084					.0861	.172						67
Plasma					.009	.008	.007	.004	.007	.004			.006	.002						
Whole blood	.0225	.079	.0267	.087	.0219	.072	.023	.075												
R.B.C.	.0175	.057	.0303	.095	.0416	.136	.0372	.122							.0151	.051				
W.B.C.	.0313	.102	.0132	.043	.0267	.087	.0202	.066							.041	.134	9	3000	3050	Hat
Plasma	.0183	.06	.0118	.038	.0081	.026	.0083	.027							.0055	.018				75
Whole blood																				
R.B.C.			.0482	.161							.0345	.115			.020	.066				
W.B.C.			.0516	.172							.0575	.192			.049	.160	5	450	3000	Lyt
Plasma			.0270	.090							.0099	.033			.006	.02				78
Whole blood																				
R.B.C.	.0113	.037	.0175	.058	.0173	.057	.0280	.093					.0115	.038	.0084	.025				
W.B.C.	.0184	.061	.0221	.073	.0230	.076	.0292	.097					.0336	.112	.0288	.095	7	3000	3000	Rog (Acute Leukemia)
Plasma	.0127	.042	.0088	.029	.0075	.025	.0035	.011					.0032	.010	.0018	.003				63
Whole blood																				
R.B.C.					.0250	.076	.026	.079							.0065	.019				
W.B.C.					.0260	.079	.031	.097							.0330	.10	8	1500	3300	Sap
Plasma					.0066	.020	.0024	.007							.0021	.006				84
Whole blood																				
R.B.C.							.116	.010			.074	.0064			.040	.0034				
W.B.C.							.062	.0053			.163	.014			.182	.0156	8	3480	11680	Tay
Plasma							.0166	.0014			.014	.0012			.008	.0007				87
Whole blood																				
R.B.C.					.017	.0697	.0155	.0635	.0148	.0607	.014	.0574								
W.B.C.					.010	.041	.0145	.0594	.0178	.0730	.016	.0656						5180	2440	Vol
Plasma					.003	.0123	.0015	.0062	.0015	.0062	.0015	.0062								90

Activities corrected for decay and to date of administration.

TABLE VIII (*Continued*)

	Name and Number of Patients Receiving P^{32} Both Orally and Intravenously	Interval in Days Between Oral and Intravenous Administrations; or I.V. and I.V. Adminis.	Name and No. of Pts. Receiving P^{32} Intravenously	Microcuries of P^{32} Administered Intravenously	Milligrams of Sodium Phosphate in Which P^{32} Was Incorporated	Periods after Intravenous Administration of P^{32}																Time (Days) for Values Under "Other"
						2 Hours		4 Hours		6 Hours		24 Hours		48 Hours		72 Hours		96 Hours		Other		
						Total	%	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%	
I. Normal Individuals																						
Whole blood						.0251	.1673			.0249	.1660	.0350	.233	.012	.080			.0058	.0386	.0037	.024	
R.B.C.			Per			.0336	.224			.0349	.2326	.0315	.210	.0198	.132			.0091	.0606	.0047	.0313	8
W.B.C.			2	1500	600	.0401	.2673			.0114	.076	.0171	.114	.016	.107			.0170	.1133	.0340	.227	
Plasma						.0096	.064			.0038	.0253	.0023	.0153	.003	.0207			.0019	.0126	.0009	.0060	
Whole blood						.0260	.1733			.0257	.1713	.0168	.112					.0033	.022	.0042	.028	
R.B.C.			Vic			.0340	.2266			.0352	.2346	.0283	.1886					.0117	.078	.0071	.047	8
W.B.C.			4	1500	600	.0274	.1822			.0110	.0733	.0113	.0753					.0168	.112	.020	.133	
Plasma						.0131	.0873			.0028	.0186	.0036	.024					.0026	.0173	.0013	.008	
III. Lymphoid Leukemia																						
Whole blood										.0208	.15			.018	.13	.0132	.09					
R.B.C.	Dry									.0328	.24			.0183	.13	.012	.08					
W.B.C.	71	10		1360	150					.0785	.59			.0546	.43	.0590	.46					
Plasma										.008	.06			.0067	.04	.0048	.02					
Whole blood						.0145	.26	.0143	.26	.0118	.21	.045	.21					.0096	.17			
R.B.C.	Gra					.0220	.40	.0245	.50	.0250	.46	.0234	.43					.0148	.27			
W.B.C.	74	6		540	150	.0188	.34	.0328	.60	.0214	.39	.0165	.30					.022	.40			
Plasma						.0076	.14	.0055	.10	.0041	.07	.0022	.04					.0011	.02			
Whole blood														.0413	.0826			.0342	.068			
R.B.C.	Sad.																	.0544	.011			
W.B.C.	82	11		5000	450									.150	.300			.1321	.264			

TABLE VIII (*Continued*)

W.B.C.	82			3000	450									.150	.300			.1321	.264				

TABLE VIII (*Continued*)

Plasma														.0118	.0236			.0047	.009				
Whole blood												.046	.242	.0425	.223					.0301	.159		
R.B.C.			Brig (Acute Leukemia) 55	1900	150							.0788	.410	.0462	.243					.0371	.195	5	
W.B.C.												.2180	1.15	.2014	1.06					.202	1.06		
Plasma												.0106	.056	.0099	.0520					.008	.0437		
Whole blood												.0281	.141					.0236	.118				
R.B.C.			Iudi (Acute Leukemia) 61	1998	180							.0251	.126					.0172	.0861				
W.B.C.												.0725	.362					.0800	.3990				
Plasma												.0071	.0356					.0061	.0305				
Whole blood																.0419	.1610						
R.B.C.			Lea 77	2600	300											.0592	.228						
W.B.C.																.1234	.475						
Plasma		30														.0129	.0496						
Whole blood																.0227	.087						
R.B.C.			Lea 77	2600	2000											.0380	.1470						
W.B.C.																.0810	.3110						
Plasma																.0080	.0310						
Whole blood												.0380	.170			.0690	.3050			—	—		
R.B.C.			Port 81	2250	300							.080	.356			.0394	.1750			.0236	.1050	8	
W.B.C.												.0954	.424			.1120	.4980			.177	.790		
Plasma		27										.0090	.040			.008	.036			.0117	.052		
Whole blood												.0251	.1120			.0193	.0859			.0099	.044		
R.B.C.			Port 81	2250	2000							.0514	.228			.0334	.1480			.0183	.0814	8	
W.B.C.												.0780	.3470			.1352	.601			.1105	.4910		
Plasma												.0070	.0311			.0056	.0249			.0030	.0133		
Whole blood						.0420	.195	.0400	.1850	.0390	.1800	.038	.176			.0290	.1350			.0110	.0510	14	
R.B.C.			Youn 91	2160	180	.0570	.264	.063	.2920	.0710	.3280	.065	.300			.0510	.236			.0130	.060	←	
W.B.C.						.0460	.213	.064	.2960	.0810	.3750	.0810	.3750			.0760	.358			.121	.560		
Plasma						.0330	.153	.0210	.0970	.0160	.0740	.0070	.0320			.0080	.0350			.003	.013		

Total amounts expressed in microcuries per c.c.; percentages in % of dose per 100 c.c.

The Ringer's solution which was used as a wash for the blood cells (both white and red) contained usually less than 1 to rarely 10 per cent of the radio-phosphorus in the blood elements—an indication that the amount adsorbed on the surface of the cells or lost through handling, was minimal.

2. Excretion (table 9 and figure 2, left side).

The normal individuals excreted in urine and feces a greater percentage of administered radio-phosphorus than did the patients. And after the forty-eighth hour more P^{32} was excreted in the urine than feces of the normal individuals and there is no reason to assume that this does not continue until all of the P^{32} absorbed by the body is ultimately and eventually excreted. The patients apparently excreted P^{32} more slowly—at least the average rate of excretion of the patients was slower than that of the normal individuals.

As would be expected, a greater quantity of P^{32} was excreted in the feces than in the urine. The P^{32} in the feces was made up of that not absorbed by the gastrointestinal tract and that which was excreted after absorption.

The total percentage of P^{32} excreted in the urine and feces of the normal individuals during the six days following its oral administration varied from: 22.9 to 46.3 per cent of the dose administered; of the myeloid leukemia patients during four to six days after administration: 14.1 to 45.5 per cent; and of the lymphoid leukemic patients: 37.8 to 53.9 per cent.

C. Intravenous Administration of Radio-Phosphorus.

1. Absorption (tables 7 and 8 and figure 1, right side).

The absorption rates following intravenous administration of radioactive phosphorus to 2 normal individuals and 16 patients (2 acute and 14 chronic cases) were not identical with those noted following oral administration. The levels of radio-phosphorus in the plasma during the first few hours after intravenous administration were slightly higher and the content of radio-phosphorus in the peripheral red blood cells rose more rapidly to considerably higher levels. As can be observed, the leukemic white blood cells took up more quickly and retained greater amounts of P^{32} than did the normal white blood cells. The white blood cells of the normal individuals retained only slightly greater amounts of P^{32}, when it was administered intravenously than when orally; while the leukemic cells retained considerably greater amounts following the intravenous administration.

2. Excretion (table 9 and figure 2, right side).

Small and nearly equal amounts of P^{32} were excreted in the feces of both normal individuals and patients. But the former group excreted more P^{32} in the urine during the first 48 hours than was excreted by the latter group during the same period. The normal individuals excreted more P^{32} in the urine following its intravenous than its oral administration, but this was not true for the patients.

After the period of 48 hours following administration, both groups excreted in the urine and feces similar amounts of P^{32} and this undoubtedly continued until all of the P^{32} absorbed by the cases was ultimately excreted.

During the six days following the intravenous administration of P^{32} the normal individuals excreted from 26.1 to 50.5 per cent of the dose administered; during the four to six days the patients with myeloid leukemia excreted from 5.6 to 24.5 per cent, those with lymphoid, 2.79 to 16.5 per cent.

In summary, therefore, the normal individuals excreted during the period studied about the same amount of P^{32} regardless of route of administration, while the patients excreted, during a similar period, much less when P^{32} was administered intravenously than when orally. The rate of excretion differed in the two groups. Regardless of the route of administration the normal persons excreted P^{32} much more rapidly in the urine and feces than did the patients during the first 48 hours after administration. After that interval, the rates were similar in both groups. In most instances, following the 48-hour period, more P^{32} (quantitatively) was excreted in the urine than in the feces in both groups.

D. Introductory Remarks on Clinical Results.

Since the clinical application of artificially produced radioactive agents is still in the experimental stage the majority of patients treated with radiophosphorus were those who had previously received x-radiation and Fowler's solution. Many of them were in the terminal stages of their disease processes. Until sufficient knowledge of diffuse neoplastic or near-neoplastic diseases has been gained so that their prevention is possible, radiations of various types seem to be the best therapy available for alleviating the symptoms which result. As is well known, some patients with leukemia respond favorably to x-radiation and others do not; similarly, as seen from the experiences related in this report, some respond favorably to the beta-rays of radio-phosphorus while others do not. Radiations which produce sufficient ionization can kill cells. Among other factors, effective therapeutic ionization depends upon the intensity and energy of the radiation in question, the penetrability of the radiation (which depends upon the density of the object irradiated), the constancy or duration of the radiation, and the position or localization of the ionization produced by the radiation.

Among the many types of x-radiation therapy used for leukemia there are: (1) the technic in which 100,000 to 400,000 volt roentgen-rays are directed toward the spleen, the peripheral nodes or the long bones; the single dose varying between 50 to 200 r; (2) the Heublein [4] technic, which consists of the use of small amounts of high voltage (150 to 200 k.v.) x-radiation over prolonged periods (7 to 21 days) to the whole body at long distances (15 to 20 feet); the total dose varying between 200 to 400 r during a 2-week period (average of about 20 r per 24 hours); and (3) the "spray" [28] technic, which consists of the use of high voltage x-radiation directed towards the whole body (alternately front and back) at 50 to 100 cm. distance; the total dose varying between 50 to 60 r which is given in a few minutes of time. Unlike roentgen-rays, which penetrate many centimeters of water, the beta-

TABLE IX

Rates of Excretion of Radio-Phosphorus in Urine and Feces

	Periods after Oral Administration of P^{32}														Milligrams of Sodium Phosphate in Which P^{32} Was Incorporated	Microcuries of P^{32} Administered Orally	Name and Number of Patients Receiving Radio-Phosphorus Orally
	1 Day		2 Days		3 Days		4 Days		5 Days		6 Days		Total Excretion				
	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%	Total 4–6 Days	%			
I. Normal Individuals																	
Urine	69.5	4.63	25.5	1.7	13.4	.89	10.9	.72	11.1	.74	6.75	.45	344	22.9	600	1500	Mie
Stool	194.	12.93	7.8	.52	3.32	.22	.41	.02			.95	.06					1
Urine	191.19	12.7	29.5	1.96	31.8	2.12	17.34	1.15	21.22	1.41	16.9	1.12	695	46.3	600	1500	Rob
Stool	338.98	22.59	38.8	2.59	5.85	.39	3.05	.10	.14	.01	.18	.01					3
II. Myeloid Leukemia																	
Urine	275.	7.15	56.8	1.47	37.1	.964	29.0	.754					545	14.1	930	3850	Beac
Stool			82.	2.13	56.	1.45	9.2	.239									14
Urine	730.8	5.8	226.8	1.8	201.6	1.6	189.	1.5	176.4	1.4	176.4	1.4	2898	23.0	20	12600	That
Stool	844.2	6.7	189.	1.5	126.	1.0	25.2	.2			12.6	.1					45
Urine	255.	6.37	63.	1.57	41.8	1.45	24.5	.61					831	20.8	1000	4000	Cole
Stool	.47	.01	270.	6.75	158.	3.97	18.7	.46									17
Urine	163.9	3.49	35.76	.76	29.8	.635	28.62	.571	26.82	.571	26.82	.571	814	17.3	3000	4700	Ebey
Stool	238.4	5.18	59.6	1.27	53.64	1.14	50.66	1.08	50.66	1.08	50.66	1.08					19

TABLE IX (*Continued*)

Urine	35.76	.6	17.88	.3	11.92	.2	11.92	.2	25.96	.1	25.96	.1	1488	25.1	2800	5960	Hay 97
Stool			911.9	15.3			447.	7.5									
Urine	564.	12.	239.7	5.1	42.93	.9	38.16	.8	32.39	.7	32.39	.7	2134	45.4	3000	4700	Ken 27
Stool	987.	21.	164.5	3.5			23.85	.5			9.54	.2					
Urine	19.08	.4	47.7	1.	28.62	.6	23.85	.5	19.08	.4	19.08	.4	1712	35.9		4700	Welc (Ac. Leuk)
Stool	858.6	18.			572.4	12.	33.39	.7			90.63	1.9					

TABLE IX (*Continued*)

	Name and Number of Patients Receiving P^{32} Orally and Intravenously	Interval in Days Between Oral and Intravenous Administrations	Name and Number of Patients Receiving Radiophosphorus Intravenously	Microcuries of P^{32} Administered Intravenously	Milligrams of Sodium Phosphate in Which P^{32} Was Incorporated	Periods after Intravenous Administration of P^{32}																			
						15 Min.		2 Hours		4 Hours		1 Day		2 Days		3 Days		4 Days		5 Days		6 Days		Total Excretion	
						Total	%	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%	Total 4–6 Days	%
I. Normal Individuals																									
Urine			Per	1500	600							565.2	37.66	75.5	5.03	37.3	2.48	25.41	1.69	26.16	1.74	17.49	1.16	760	50.5
Stool			2									1.47	.098	3.87	.25	3.72	.24	2.49	.16	.35	.02	.77	.05		
Urine			Vic	1500	600							250.	16.66	52.5	3.5	22.6	1.5	22.2	1.48	19.11	1.27	16.	1.06	391	26.1
Stool			4									1.29	.08	5.74	.45					.30	.02	.15	.01		
II. Myeloid Leukemia																									
Urine	Beac	7		870	150							27.9	3.21	8.65	.99	6.6	.75	5.	.57					49	5.61
Stool	14													.51	.05							.30	.03		
Urine	That	240		1140	150					8.5	.74	21.5	1.88	10.6	.92		1.6	14.4	1.2	2.7	.23			85	7.5
Stool	45											3.62	.31	2.26	.19	1.37	.12	1.12	.09						
Urine			Klin	1950	300	25.2	1.29					310.	16.05	64.2	3.29	45.0	2.39	33.8	1.93					478	24.5
Stool			28																						
Urine			Park	1260	150							11.2	.88	63.5	5.03	125.	9.91	2.36	.18					214	16.9
Stool			39									2.5	.19	1.09	.08	5.5	.43	2.58	.20						

TABLE IX (*Continued*)

Urine																								
Stool																								
Urine																								
Stool																								
Urine																								
Stool																								

III. Lymphoid Leukemia

Urine	Dryd 71	10		1360	150	24.9	1.83	22.3	1.63			24.4	1.79	26.0	1.91	7.7	.56	9.1	.66	8.6	.63			128	9.41
Stool								1.55	.11	.81	.05									1.95	.14				
Vomites										.845	.06														
Urine	Grah 74	6		540	150	5.2	.96			21.4	3.96	17.	3.15	11.6	2.14	8.5	1.57	9.	1.66					89.0	16.5
Stool																13.1	2.2	3.17	.58						
Urine			Brig (ac. leuk) 55	1900	150							63.6	3.35	44.9	2.36	.92	.048	15.44	.813	14.5	.763			145.6	7.66
Stool														6.24	.328										
Urine			Iudi (ac. leuk) 61	1998	180							48.3	2.42	4.05	.203	1.69	.085	.573	.029					55.87	2.79
Stool																1.26	.063								
Urine			Sadl 82	5000	450							442.	8.84	138.4	2.77	97.2	1.94	87.2	1.75					813.5	16.3
Stool												1.10	.002	8.2	.164	13.1	.262	26.2	.524						
Urine			Youn 91	2160	180	8.1	.37	95.5	4.42			121.6	5.62	32.4	1.5	20.8	.97	19.3	.89	7.65	.35	8.75	.4	350	16.3
Stool						.03	.001							1.05	.04	.79	.03	7.6	.35	12.	.55	14.6	.68		

Total amounts and percentages of doses expressed in microcuries.

rays emitted by radio-phosphorus penetrate less than 1 cm. of water, but both cause ionization in body tissues. However, the radio-phosphorus atom localizes in the body cells themselves and may remain there for prolonged periods. Therefore x-radiation given by technic (2) is more comparable to the beta radiation of P^{32} than technics (1) and (3).

E. Clinical Results.

The clinical results are recorded in tables 1 to 6. A summary of the results of the two large groups of patients (tables 2 and 3) follows:

Type of Disease	Myeloid Leukemia		Lymphoid Leukemia	
	Acute	Chronic	Acute	Chronic
No. of cases	8	38	16	25
No. of partial remissions	0	11	1	8
No. of complete remissions	0	5	1	1
No. dead	8	21	15	13

The duration of the partial and complete remissions and the various time intervals involved are indicated on the tables. Two patients (cases 27 and 30) have had essentially complete remissions for nearly two years. We have failed to find other examples in the literature of authentic cases of leukemia with complete remissions of two years' duration. As is well known, both complete and partial remissions may occur spontaneously and many remissions of a rather prolonged nature have been reported following transfusions, infections and the administration of various specific agents (H. W. Jones, F. R. Miller and W. A. Hause, Trans. Assoc. Am. Phys., 1940, lv, 54) or less specific ones such as adenylic acid and nucleotides. One of us (L. A. E.) has observed temporary but complete remissions in 3 patients with leukemia following transfusion of blood of donors who were suffering with symptoms of mild influenza. It is unfortunate that the percentages of partial and complete remissions of all cases of leukemia recorded in the literature are not known.

Of 10 patients with chronic lymphoid and 12 with chronic myeloid leukemia who had had no therapy previous to that of radio-phosphorus, 4 in each group died (3 in the former group and 1 in the latter were moribund when P^{32} was first administered) while the other 14 had either partial or complete remissions of six months to a year in duration. The results in those patients who had had x-radiation previously to the administration of radio-phosphorus are not so encouraging, and it is from this experience that we feel that x-radiation reduces the effectiveness of radio-phosphorus since the duration of the disease processes previous to administration of radio-phosphorus was quite similar in both groups just mentioned.

Although the physical and symptomatic changes are indicated on the tables (1 to 4) all of the hematological changes cannot be. Therefore table 10 lists in some detail the blood findings of 10 patients with lymphoid

and 10 with myeloid leukemia and one with a leukemoid reaction which are among those with interesting changes. (Two of the cases (numbers 56 and 88) with lymphoid leukemia, listed in table 10, and case 43 with myeloid leukemia, table 2, were given neutron radiation, produced by the deuteron beam of the cyclotron directed against beryllium. The hematological responses were satisfactory. This opens a new field for the investigation of the clinical response of patients with leukemia to whole body irradiation with neutrons.) By examining the results recorded on table 10 one can observe that in many instances the white blood cell levels decreased, the differential

TABLE X

Blood Levels Following Administration of Radio-Phosphorus

Case No. / Name / Sex / Age	Inclusive Dates of Administration	Amount (Mc) and Route of P^{32} or Neutron Therapy Adm.	Dates of Blood Counts	Hb per cent (Sahl	RBC in 10 Thousands	WBC in Thousands	Pl in Thousands	Differential							
								Seg. Polys.	Non-Seg. Polys.	Myelocytes	Myeloblasts	Lymphocytes	Lymphoblasts	Monocytes	Others
A. Myeloid Leukemia															
14 Beac. M 45	5/22/40 to 9/25/40	.87 (I.V.) 14.31 (0)	5/ 6/40	59	296	164	200	34	14	46	1	3	—	—	2
			7/19/40	93	469	80	600	14	38	41	1	2	—	—	4
			11/12/40	96	507	11	260	62	8	14	—	12	—	—	2
			2/10/41	110	628	10	700	67	9	—	—	21	—	—	3
17 Cole. M 23	5/27/40 to 1/ 8/41	19. (0)	5/23/40	81	405	148	200	40	19	35	4	2	—	—	—
			1/ 8/41	110	597	38	238	51	10	14	—	2	—	14	9
22 Hall. F 49	10/ 7/40 to 12/27/40	16.9 (0)	10/ 7/40	67	275	380	414	10	36	46	2	1	—	—	5
			1/28/41	100	541	124	334	26	36	32	—	4	—	—	2
			3/ 5/41	111	567	67	400	23	33	29	—	7	—	—	7
27 Kenn. M 21	11/29/38 to 6/ 7/39	10.72 (0)	11/ 4/38	86	342	200	720	32	25	29	1	6	—	3	4
			5/ 4/39	89	462	35	260	41	24	19	—	11	—	1	4
			8/ 1/39	96	448	12	205	51	9	9	—	20	—	7	4
			1/ 9/40	100	438	13	150	67	9	1	—	21	—	1	1
			2/26/41	105	510	11	175	52	8	—	—	22	—	10	8
28 Klin. M 31	6/13/40 to 11/23/40	1.95 (I.V.) 17 (0)	5/13/40	76	—	103	—	45	17	31	4	—	—	—	3
			6/24/40	88	510	67	253	60	18	17	—	—	—	1	3
			12/16/40	94	—	67	—	—	—	—	—	—	—	—	—
29 Kret. M 11	7/14/39 to 2/ 4/41	28 (0)	7/16/39	56	354	380	—	20	17	59	2	2	—	—	—
			12/22/39	74	365	6	—	40	45	4	—	—	—	—	1
			7/22/40	95	517	10	—	43	5	7	—	38	—	4	3
			1/28/41	90	480	8	—	29	35	15	—	18	—	—	3
			2/ 4/41	68	410	6	—	24	43	22	9	—	—	—	1
			2/16/41	(Died)											
30 LaV. F 44	1/ 4/39 to 2/17/41	21.72 (0)	6/10/35	75	—	208	—	—	—	—	—	—	—	—	—
			12/ 7/38	99	402	30	448	41	11	21	1	14	—	5	7
			5/15/39	103	470	65	530	51	16	9	2	12	—	4	6
			11/17/39	97	395	18	470	54	12	14	2	10	—	2	6
			2/23/40	100	458	6	335	41	11	2	—	31	—	6	9
			3/ 4/41	94	572	12	500	66	5	7	—	14	—	—	8
33 Mars. F 11	4/13/40 to 2/19/41	17.17 (0)	4/16/40	88	476	125	105	14	23	53	2	—	—	—	8
			7/31/40	106	583	42	50	44	9	21	—	13	—	4	9
			2/ 8/41	100	515	27	100	50	6	23	—	15	—	5	1
35 Mont. M 37	6/27/40 to 1/23/41	32 (0)	6/20/40	80	390	147	—	59	21	18	1	—	—	—	1
			1/31/41	87	430	14	300	44	14	—	—	38	—	2	2
			3/ 6/41	98	512	9	—	44	5	—	—	37	—	3	11
37 Nuti. M 57	5/ 2/40 to 2/18/41	9.7 (I.V.) 25.52 (0)	5/ 3/40	68	354	368	358	20	19	51	3	—	—	1	6
			3/ 4/41	87	438	74	200	30	37	26	—	—	2	—	5

TABLE X (*Continued*)

Case No. Name Sex Age	Inclusive Dates of Administration	Amount (Mc) and Route of P^{32} or Neutron Therapy Adm.	Dates of Blood Counts	Hb per cent (Sahli)	RBC in 10 Thousands	WBC in Thousands	Pl in Thousands	Differential							
								Seg. Polys.	Non-Seg. Polys.	Myelocytes	Myeloblasts	Lymphocytes	Lymphoblasts	Monocytes	Others
B. Lymphoid Leukemia															
56 Crew. F 3	12/18/40 to 1/27/41	45 N	11/25/40	41	285	3	84	17	1	—	—	76	2	4	—
			1/ 3/41	49	227	1	22	8	12	—	—	74	2	4	—
			1/ 8/41	46	210	3	96	42	27	—	—	29	—	2	—
			2/ 7/41	96	435	5	156	38	13	—	—	36	—	8	5
			3/12/41	96	592	6	130	39	33	5	—	18	—	3	3
57 Fier. M 8	11/24/40 to 11/29/40	2.0 (I.V.)	10/24/40	67	380	40	10	1	—	—	—	99	—	—	—
			12/13/40	57	320	4	90	2	25	—	—	71	—	—	2
			1/29/41	44	222	1	10	2	2	—	—	87	8	—	1
			2/25/41	(Died)											
71 Dryd. M 55	5/11/40 to 1/ 2/41	1.36 (I.V.) 21.2 (0)	5/ 2/40	94	535	195	210	7	5	—	—	88	—	—	—
			10/ 7/40	114	475	70	—	6	5	—	—	88	—	1	—
			1/23/41	108	484	35	—	11	5	—	—	76	—	5	3
			2/13/41	94	481	20	—	11	4	—	—	78	—	4	4
74 Grah. F 47	4/29/40 to 1/22/41	4.5 (I.V.) 22.74 (0)	4/23/40	97	429	101	214	5	1	—	—	93	—	1	—
			7/ 1/40	97	430	47	235	9	4	—	—	86	—	1	—
			12/ 9/40	99	463	34	148	2	2	—	—	90	—	5	1
			2/18/41	97	555	27	133	3	5	—	—	88	—	5	2
75 Hatf. M 72	2/21/40 to 3/18/41	59.7 (0)	2/20/40	97	477	110	150	2	2	—	—	91	3	2	—
			6/24/40	71	310	33	91	2	3	—	—	95	—	—	—
			10/ 9/40	68	423	29	80	4	1	—	—	88	—	2	5
			2/18/41	61	376	54	—	3	1	—	—	93	—	—	3
76 Hoag. M 66	8/18/39 to 1/ 3/41	4.8 (I.V.) 20.12 (0)	7/ 6/39	62	232	223	—	2	4	—	—	94	—	—	—
			8/18/39	50	220	51	22	2	1	—	—	96	—	1	—
			10/ 9/39	72	260	12	95	21	8	—	—	60	—	8	3
			3/27/40	86	386	13	139	32	5	—	—	52	—	6	5
			9/13/40	99	401	9	278	37	4	—	—	54	—	—	5
			2/25/41	92	477	9	85	42	7	—	—	35	—	15	1
80 Mick. M 55	2/ 9/39 to 3/ 9/40	59.42 (0)	2/ 3/39	68	326	115	90	3	3	—	—	92	2	—	—
			8/18/39	90	434	41	115	24	4	—	—	59	—	4	9
			3/ 4/40	86	424	11	100	27	9	—	—	61	—	—	3
83 Sang. M 59	12/31/39 to 8/19/40	33.63 (0)	12/28/39	43	250	21	210	21	11	—	—	60	6	—	2
			5/ 1/40	62	346	7	103	32	15	—	—	40	—	8	5
			11/19/40	70	309	10	253	28	19	—	—	47	—	5	1
			3/11/41	66	315	7	321	22	24	—	—	46	—	4	4
88 Todd. M 45	11/29/40 to 1/31/40	50 N	11/13/40	111	535	59	321	—	2	—	—	85	11	—	2
			12/23/40	111	541	23	346	20	12	—	—	61	6	—	1
			2/13/41	110	558	21	—	35	24	—	—	31	4	6	—
91 Youn. M 67	4/12/40 to 1/12/41	2.6 (I.V.) 24 (0)	4/11/40	99	442	68	140	9	3	—	—	86	—	—	2
			7/ 1/40	80	414	21	160	2	6	—	—	90	—	—	2
			2/19/41	60	33	1	54	2	3	—	—	95	—	—	—
C. Leukemoid Reaction															
97 Heyd. M 59	2/26/40 to 3/21/40	15.16 (0)	2/14/40	110	525	55	256	40	40	16	1	4	—	—	—
			3/19/40	90	528	44	—	61	8	25	—	5	5	—	—
			8/ 6/40	100	587	18	—	77	10	2	—	8	—	2	1
			12/ 5/40	110	—	14	—	—	—	—	—	—	—	—	—
			3/ 6/41	115	—	26	—	64	11	—	—	21	—	4	—

counts improved and the hemoglobin levels rose following the administration of radio-phosphorus.

In general, the clinical response of patients with acute types of leukemia to radio-phosphorus is as unsatisfactory as is that following other types of

therapy but in chronic cases the results are as good if not better than those following any other type of therapy.

F. Autopsy Findings.

The radioactivity assays of the tissues obtained at autopsy will be reported elsewhere.[5] The gross findings were typical of those usually described for leukemia. The microscopic findings were interesting in that there were no cellular changes in normal cells that could be attributed to local irradiation due to deposition of radio-phosphorus. In many sections cellular lysis or rhexis was observed in leukemic cells, however. A finding of interest, which is usually not considered seriously in the pathology of leukemia, was the presence of varied degree of infiltration of the mucosa and submucosa of the gastrointestinal tract with leukemic cells in the majority of the patients with lymphoid leukemia,[29] and many with myeloid leukemia.[14] In cases 84 and 87 the infiltration in the mucosa and submucosa was sufficiently severe to permit perforation of the intestinal wall. Mild diverticulitis was present in the latter patient, who died of a *B. coli* septicemia. The kidneys and adrenals of the cases with myeloid leukemia were seldom infiltrated with leukemic cells while those of cases with lymphoid leukemia were frequently infiltrated. Only two of the patients (cases 85 and 99) showed infiltrations in the brain. (In fact, only two patients—cases 70 and 82—complained of neurological symptoms.)

The conclusion may be drawn that the amounts of radio-phosphorus so far administered have not morphologically altered normal tissues.

Discussion

Leukemia is a fatal disease characterized clinically and pathologically by various well-known alterations of the hematopoietic system.[10] It varies from a truly malignant, irreversible invasive process to a rather mild cellular infiltrative process in which complete hematological and clinical remissions may occur for periods of 6 to 12 months.* The more acute types of leukemia occur frequently in children, presumably because it is generally accepted that children have more growth promoting substances. The pathological states classified under the term " leukemia " probably are of as many types and have as many causes as the pathological states listed under the term " infection." Occasionally leukemoid reactions may be indistinguishable from true leukemia both clinically and hematologically, but these processes are completely reversible when the primary etiological agent is removed.

Some of the features other than those associated with radio-phosphorus observed during the course of this study are noteworthy. As has been noted in the investigations of others who work in the northern hemisphere, and

* Among the various types of leukemic blood cells, many presumably are mutants with excessive growth capacities. In case 63 the lymphoid cells of the peripheral blood had sufficient characteristics of malignant growth to make possible their cultivation on artificial media for indefinite periods of time. The patient lived only six months after the onset of the disease. In cases 71 and 75 lymphoid leukemic processes have existed 12 and 11 years respectively, and reproduction of their white blood cells on artificial media did not occur.

in the majority of the cases of leukemia listed here (63 out of 91), the onset of the clinical symptoms frequently occurs during winter or spring. Webster,[38] Sabin and Duffy[31] and Brues[2] have shown that among other things, inadequate diets lower resistance to disease. Rhoads et al.[30] have shown that inadequate diets predispose dogs to indol-induced anemia. Lewisohn et al.[23] were able by injections of yeast extract to cause complete regressions in 25 per cent of spontaneous breast adenocarcinomata of mice. Suguira, Rhoads, Kensler et al.[33, 16] have produced partial protection in rats against liver cancer caused by butter yellow with riboflavin with casein and with rice bran and yeast extract. Lavik and Baumann[17] have increased the incidence of hydrocarbon-induced skin cancer of mice 50 per cent by feeding diets high in various fats and oils. J. B. Mider and J. White found that mice painted with methycholanthrene would develop leukemia when fed a diet rich in sulfur containing amino acids, but would develop arteriosclerosis when fed a diet poor in such acids (the paper will appear in the Jr. of the Nat. Cancer Inst.) It is well known that during the winter months the diets consumed by human beings living particularly in the central and northern portions of the northern hemisphere are nutritionally inferior to those consumed during the summer months. Human white blood cells reproduce rapidly; the average span of life of white cells is but about four days. Nutritional deficiencies which would be of short duration such as those that follow periods of emotional trauma or nervousness would be more apt to effect cellular abnormalities in those cells frequently undergoing mitosis than in those that do not reproduce rapidly. Ussing[36] has shown that in rats 10 per cent of liver protein and about 2.5 per cent of muscle protein are newly formed from the food absorbed in the course of three days of feeding. Marshak[26] has shown that mouse leukemic cells and presumably regenerating liver cells double in number every 56 hours. From these data it is possible to deduct that a factor in the diet or a lack of some factor, could initiate hybrid formation of rapidly developing white blood cells; and that possibly certain foods could prevent or inhibit the initiation of hybrid formation.

A. *Diet.*

In view of this deduction many of the patients presented here were questioned regarding their diets. It was noted that many of them ate what may be considered a poor diet. A diet was considered inadequate if it contained only cooked muscle meats, cooked fruits and vegetables, highly processed breads and pastries, and processed or pasteurized milk. In other words, no raw foods or living cells were consumed. An adequate or "mixed" diet was considered as one that contained daily, among other foods, at least some of the following: rare muscle meats, glandular meats (sweetbreads, liver, kidney, tripe, brain, mixed sausages, giblets, etc.), raw oysters, strong cheeses containing molds and bacteria (as Roquefort and Camembert), uncontaminated raw milk, coarse breads and raw vegetables and fruits. In eliciting the dietary history, all foods consumed were considered.

This classification of diets is subject to many criticisms but it is an initial attempt to note dietary differences. Of the eight patients with acute myeloid leukemia, three regularly consumed the "mixed" diet for years previous to the onset of the symptoms of leukemia; four regularly consumed the inadequate diet; and one was not questioned. Of 38 with chronic myeloid leukemia, three consumed the "mixed" diet; 25 the inadequate diet; and 10 were not questioned. Of the 16 with acute lymphoid leukemia, one took a "mixed" diet, three an inadequate diet, and 12 were not questioned. Of the 25 with chronic lymphoid leukemia, three took a "mixed" diet, 20 an inadequate diet, and two were not questioned. The ability of the patients to store various nutrients obviously was impossible to elicit. The enormous numbers of human beings who consume so-called inadequate diets but in whom leukemia does not develop of course would be impossible to determine.

In summary, it has been observed that many patients with leukemia consumed diets previous to the onset of leukemia which were considered inadequate and that in the majority of the patients the symptoms of leukemia developed during the winter months when the diet is most likely to be inadequate for short periods of time, at least. Poor or inadequate nutrition may initiate cellular abnormalities or may lower "resistance" of regenerating cells to various poisonings (benzene,[11] benzene ring compounds, carcinogens, etc.) which in turn may lead to the formation of abnormal cellular hybrids. It is known that once an irreversible neoplastic process has been initiated and established, adequate nutrition enhances rather than reverses its growth. If leukemia is such a process initiated by a deficiency, the addition of the deficient agent to the diet would probably not alter the course of an established leukemic process.[3, 27]

B. *Gastrointestinal Tract.*

Another feature observed was the occurrence of episodes of diarrhea or attacks of "slimy stools" in a rather high percentage of patients with lymphoid leukemia. It occurred much less frequently in those with myeloid leukemia. The attacks were irregular in duration and intensity but frequently preceded relapse or an acceleration of the leukemic process. Of 25 patients with chronic lymphoid leukemia, 14 had attacks of diarrhea or slimy stools during the course of the disease, six did not, and five were not questioned. Of 16 patients with acute lymphoid leukemia, four had attacks of diarrhea, one had none and 11 were not questioned. Among the 46 patients with acute and chronic myeloid leukemia, only five of the 28 questioned had episodes of diarrhea. As was stated above, the sub-mucosa of the gastrointestinal tract of patients with lymphoid leukemia often becomes variably infiltrated. Since there is some evidence that the majority of the lymphocytes may be produced in the submucosa of the gastrointestinal tract,[6] the process of lymphoid leukemia may originate by the abnormal production and release of the lymphocytes from this region; and an abnormal excretion of lymphocytes may be responsible for the occurrence of "slimy stools." Of

the four patients (cases 52, 62, 63 and 72) with ascites, due probably to congestion of the lymphatic system of the gastrointestinal tract, all suffered with lymphoid leukemia. It is concluded that the gastrointestinal tract may play a significant rôle in leukemia, particularly lymphoid leukemia.

C. *Associated Disease.*

Many observers have reported that various diseases or conditions preceded or were associated with leukemia. Similar associated conditions were noted in the group of patients included in this report. In 12 patients (cases 11, 25, 29, 36, 45, 48, 58, 72, 74, 75, 82 and 86) the onset of leukemia was preceded by symptoms of influenza. In eight (cases 5, 19, 22, 28, 30, 43, 71 and 88) the onset was preceded or associated with dental symptoms (toothache, loose teeth, etc.). In two (cases 16 and 36) the disease process was noted near the end of the term of pregnancy.[7] In six (cases 33, 46, 47, 48, 71 and 90) trauma [24, 39] (fractures, various accidents) had occurred previous to the onset of symptoms. In 10 (cases 7, 25, 32, 33, 54, 55, 56, 60, 65 and 95) rarefaction of bones was found upon roentgenological examination early in the course of the disease. The work of Iwatsura and Nanjo,[12] who noted particularly a marked increase in phosphatase activity of the serum of patients with myeloid leukemia, offers an explanation for the rarefaction of bones and loose teeth which occur occasionally in the myeloid type of the disease. Increased concentrations of serum-phosphatase may "open" healed calcified tubercles. Five patients (cases 14, 20, 41, 46—myeloid, and 81—lymphoid) had had active tuberculosis [13] but the pulmonary tubercles had been well walled off as indicated by roentgenological pictures several years preceding the onset of symptoms of leukemia. However, two (cases 41 and 46) of these patients after the onset of myeloid leukemia developed a diffuse density of the lungs and at autopsy diffuse miliary tuberculosis was found. The other three patients are being watched closely. Four patients (cases 24, 31, 63 and 81) were vaccinated during the course of the disease and the reactions were extremely severe. In two of these cases most of the dorsal aspect of the vaccinated arm sloughed off before death and the other two patients developed large necrotic areas which had not healed six months after vaccination.

D. *Benzene.*

Another possible etiological factor to which increasing weight is being given is the rôle played by compounds which prominently contain the benzene ring.[11] Many cases of leukemia following exposure to benzene [9] and many cases with leukemoid reactions following treatment with substances in which the benzene ring is prominent have been reported in the recent literature. Three patients (cases 58, 74 and 78) of the group herein reported as well as three patients observed more recently, had ingested large amounts of the "sulfone group" of compounds just before the onset of the leukemic processes. One patient, not listed in this report, had a severe myeloid leukemoid reaction (hemoglobin 30 per cent, white blood count 80,000, with 35 per

cent myelocytes) following sulfanilamide therapy from which she recovered after cessation of the therapy. On the other hand, evidence has been presented [1, 25] that clinical and hematological improvement occurs in patients with leukemia following the administration of sulfapyridine. Three patients (cases 10, 46 and 81) had been painters, one (67) had been a printer and in addition took 2 N. R. tablets daily for 10 years, another (82) took mineral oil daily for 5 to 6 years preceding onset of leukemia. One patient (32) worked for 18 years in a benzol refinery, and another (88) together with a crew associate simultaneously developed chronic lymphoid leukemia after both had worked for a period of 10 years' duration in engine rooms of U. S. Navy submarines.

E. *Sunlight.*

A number of patients (cases 42, 54, 69, 71 and 75) apparently experienced symptomatic and even hematological improvement following exposure to sunlight.[32] The number of circulating white blood cells can be influenced by the rays of the sun, by roentgen-rays, by beta rays, by neutron rays, by ultra-violet rays, etc.

F. *Heredity.*

Since the influence of heredity on leukemia has been widely discussed, from both clinical and experimental standpoints it is merely mentioned here. Case 38 had a maternal aunt and a cousin (son of the aunt) both of whom died of leukemia. All three had the myeloid type of the disease and in each case the duration of the disease was three years. A maternal aunt of case 7 and the mother of case 88 died of leukemia. The daughter of case 76 has developed splenomegaly at the time of this writing.

In summary, the foregoing discussion indicates that both intrinsic or hereditary and extrinsic or environmental factors may be involved in the etiology of leukemia and suggests, as is well known, that there is some fundamental underlying change responsible for the onset of leukemia which so far is not understood.

Conclusions

1. The rates of absorption of radio-phosphorus, for four to eight days following "therapeutic" doses administered intravenously and orally, by the plasma, red blood cells and white blood cells of normal individuals and patients with myeloid and lymphoid leukemia, are presented (figure 1). Circulating leukemic cells retain radio-phosphorus in greater concentrations than normal circulating white blood cells.

2. The rates of excretion in urine and feces of radio-phosphorus, administered similarly and to the same groups as described in paragraph 1, are presented (figure 2). Normal individuals excrete radio-phosphorus more rapidly than patients with leukemia during the first 48 hours after administration. The rates after the 48-hour period are similar and proceed undoubtedly until all of the radio-phosphorus absorbed has been excreted.

The total percentages of P^{32} excreted by the groups for a period of 4 to 6 days following the administration of various doses are also presented (table 9).

3. Clinical and hematological results following administration of radio-phosphorus to patients with leukemia are presented (tables 2, 3, 4, 5 and 10). Radio-phosphorus is as effective as other types of treatment in general use, can be easily administered orally or intravenously, produces no nausea, weakness or anorexia following administration, and the results are sufficiently encouraging to warrant intense investigation. Two cases of leukemia with essentially complete remissions of nearly two years' duration are reported. Both are still alive at this writing.

4. In the doses described herein, radio-phosphorus produced no morphological damage to normal tissues.

5. Various intrinsic and extrinsic factors which may be associated with leukemia are discussed.

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SYMPTOMATIC HEMOLYTIC ANEMIA *

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IN their recent review of acute hemolytic anemia, Dameshek and Schwartz [7a] classify hemolytic anemia as follows:

A. Congenital
B. Acquired
1. Secondary to known cause (infectious, chemical, "toxic," pregnancy, etc.);
2. Symptomatic, in association with certain, usually malignant diseases, as lymphatic leukemia, Hodgkin's disease, carcinomatosis;
3. Of unknown cause, with or without hemolysins in the serum.

Symptomatic hemolytic anemia may be defined as a hemolytic syndrome often indistinguishable by hematological methods from the well-known picture of familial hemolytic jaundice, but showing a definite etiological relationship to such underlying diseases as neoplasm (teratoma, sarcoma), leukemia, and Hodgkin's disease. Frequently but not regularly, the pathological lesions are situated in the spleen, thus suggesting a splenic disorder. That the hemolytic process in these cases is not merely coincidental is demonstrated, at least in some instances, by the disappearance of all signs of the hemolytic process following successful treatment of the "accompanying" disorder. Thus, removal of a dermoid cyst may result in complete cure of a severe hemolytic anemia. Furthermore, symptomatic hemolytic anemia has been observed in relatively few conditions.

The clinical features of the cases of symptomatic hemolytic anemia represent a combination of the symptoms and signs of the hemolytic process and those of the underlying disease. As the latter condition may remain latent or fail to manifest itself in characteristic fashion, the predominant picture may be that of the hemolytic process. On the other hand, the underlying disease may be readily apparent, but the "accompanying" hemolytic anemia may seem difficult to reconcile with the usual symptomatology. Since hemolytic anemia is by no means a common feature of most of the underlying disorders, it has on this account usually escaped attention. Why only certain cases of Hodgkin's disease with involvement of the spleen are associated with a hemolytic syndrome is quite obscure. The correct interpretation of these cases of symptomatic hemolytic anemia is of importance not only in the practical matters of diagnosis and therapy but in the more theoretical problems

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of the pathogenesis of inherited and acquired hemolytic jaundice. This paper, which deals with the analysis of several observations of symptomatic hemolytic anemia, illustrates these viewpoints.

I. Symptomatic hemolytic anemia in association with neoplasm. Anemia, which is common in neoplastic conditions, may be of several types. The hypochromic microcytic type of iron deficiency may be the result either of hemorrhage, impaired gastric digestion or of intestinal malabsorption. Another variety of anemia occasionally seen is that due to metastatic involvement of the bone-marrow, the anemia in this instance being normocytic and usually associated with the presence in the peripheral blood of nucleated red cells and immature leukocytes. Rarely, the typical macrocytic picture of pernicious anemia is observed in some cases of gastrointestinal neoplasm in which the pathological lesion interferes with the normal mechanisms of production, absorption or utilization of the anti-pernicious anemia principle.

Not generally known, however, is the fact that neoplasms, both benign and malignant, are occasionally associated with a hemolytic spherocytic process. The following two cases demonstrate this relationship.

Case 1. Dermoid cyst (teratoma) of the ovary. T.P., a 47-year-old Jewish housewife, was admitted to the Joseph H. Pratt Diagnostic Hospital on May 8, 1939. Since the first of the year, she had noticed increasing pallor, weakness and dyspnea. Examination in May showed marked pallor and slight jaundice. There were arteriosclerotic changes of the retinal blood vessels, a rough blowing systolic murmur in the aortic area, and hypertension. Blood pressure: Systolic 198 mm. of Hg, diastolic 108 mm. The edges of both the spleen and liver were just palpable. A mass the size of an orange was felt in the region of the left ovary.

The laboratory data were as follows: Hemoglobin 34 per cent; red blood cells 1.59 million; white blood cells 10,800; platelets 646,000. The red cells showed marked spherocytosis and the reticulocytes numbered 46 per cent. Three metamyelocytes and two myelocytes were noted in counting 100 white blood cells. The mean cell volume was 78 c. micra, the mean cell diameter 6.0 micra, the mean cell thickness 2.8 micra. Hemolysis in hypotonic solutions of NaCl began at .68 per cent and was complete at 40 per cent. The lysolecithin fragility test (Singer [34a]) was normal. The urine contained no bile, but increased quantities of urobilinogen were demonstrated (1:80 by the Wallace-Diamond technic). The serum bilirubin, which was of the indirect variety, measured 5.0 mg. per 100 c.c.

On the basis of the spherocytosis and increased hypotonic fragility, the diagnosis of congenital or familial hemolytic jaundice was at first made despite the rather atypical and relatively acute onset, and the complete absence of familial hemolytic disease. The normal lysolecithin fragility was also against the familial type of disease. Splenectomy was advised.

The patient was admitted to the Beth Israel Hospital on June 28, 1939. The anemia was somewhat greater at this time, and nucleated red cells were commonly present (5–7 per 100 white blood cells). The spleen and liver were now felt two fingers'-breadth below their respective costal margins. After a single transfusion of 500 c.c. of blood, splenectomy was performed on July 6 under cyclopropane-ether anesthesia. A second transfusion was given postoperatively. Atelectasis of the left lower lung occurred the day after operation. A third transfusion was given on July 23 because the hematological response was unexpectedly slow.

By September 6, two months after operation, the red cell count had reached 4.19 million, the hemoglobin 77 per cent, and there had been striking drops in the reticulo-

cytes (4.5 per cent) and in the bilirubin content of the blood (to 0.9 mg. per cent). This improvement was short-lived, however, for in October, 1939 the patient again began to feel poorly. She was readmitted to the hospital on November 24. Examination showed jaundice of the sclerae and skin and a greatly enlarged liver which was now palpable four fingers'-breadth below the right costal margin. There was a striking drop in the red cell count—to 1.24 million—and in the hemoglobin to 24 per cent. Various procedures, such as the intravenous injection of congo red, roentgen-radiation over the abdomen, the use of large doses of liver extract and iron, were without effect. Because of the possibility of the presence of an accessory spleen, thorotrast (75 c.c.) was injected and roentgen-ray pictures taken, but no accessory spleen was demonstrated. The patient's course was steadily downhill and was interrupted only by repeated blood transfusions. In all, 24 transfusions, each of 500 c.c., were given in the period from November 24, 1939 to February 29, 1940 with only transient rises in hemoglobin and erythrocyte counts. The last series of transfusions brought the level of erythrocytes to 3.4 million and the hemoglobin to 68 per cent. At this point, it was decided that further temporizing was inadvisable and that active search must be made either for an accessory spleen or, in view of the previous observation of West-Watson and Young,[40] for a dermoid cyst of the ovary. An exploratory laparotomy was accordingly done on February 29, 1940. No accessory spleen was found, but a large round mass arising from the left ovary was discovered and removed, together with the accompanying tube. Biopsy of the liver was also performed. Following this operation, the hemolytic process gradually subsided and in about four months the hematological picture was entirely normal. Spherocytosis and the increased hypotonic fragility of the erythrocytes disappeared completely, coincidentally with an increase in the mean cell diameter from about 6 micra to 7.35 micra. The blood bilirubin content dropped to normal and the urobilinogen excretion in the feces, which had approximated 2000 mg. daily in December, also became normal (86 mg. per day).

The ovarian mass proved to be a thick-walled, unilocular dermoid cyst, 7 cm. in diameter, with a fairly smooth, pink-gray to bright pink inner membrane. In one area a rough, irregular, bony area 3 by 4 cm. in extent was found. The cyst contained thick, mayonnaise-like fluid within which was found a small tangled skein of long brown hair. The relatively large area of well-formed bone showed a small amount of tissue closely simulating bone marrow. Also present were a few dilated sweat glands, cholesterol clefts, a large mass of fat, phagocytes sprinkled with plasma cells and large mononuclear cells, and half a dozen typical lymphoid follicles each of which had an active germinal center. No definite splenic tissue was discovered. Biopsy of the liver showed infiltration of the portal spaces with large numbers of lymphocytes, definite proliferation of bile ducts, together with areas in the sinusoids containing many polymorphonuclear leukocytes. The most marked change was the increased prominence of the Kupffer cells which were filled with hemosiderin.

This case thus appears to be an example of "symptomatic" hemolytic anemia which was temporarily improved by splenectomy but in which a cure was obtained only after removal of a dermoid cyst. We believe that the complete, and thus far permanent response up to Aug. 1941 points to a definite relationship between the hemolytic process and the dermoid cyst. A strikingly similar observation was made in the case of West-Watson and Young (1938).[40] In this case, that of a 44 year old woman, there was a severe hemolytic anemia (hemoglobin 17 per cent, red blood cells 0.5 million, reticulocytes 50 per cent, marked spherocytosis and increased hypotonic fragility: 0.66–0.44). There was an elevation in the bilirubin content of

the blood which was of the "indirect" variety. Splenectomy was performed but without subsidence of the hemolytic process. Operation for the possible removal of an accessory spleen was performed and an ovarian tumor discovered, as in our case. This proved to be a teratoma, and following its removal, the patient made an uneventful and complete recovery. No splenic tissue was found in the tumor.

TABLE I

Date	R.B.C. Million per cu. mm.	Hgb. %	Reticulocytes %	Hypotonic Fragility Hemolysis Begins — Complete	Remarks
5/ 8/1939	1.59	34	46	0.68 — 0.40	Many spherocytes
6/29/ "	1.66	33	33	0.68 — 0.04	Many spherocytes and normoblasts
7/ 7/ "	1.82	38	33	0.68 — 0.04	
7/ 7/ "			*Splenectomy*		
7/ 8/ "	1.93	44	36	—	Howell-Jolly bodies
7/14/ "	2.54	43	16.5	0.68 — 0.16	
7/31/ "	3.16	58	10	0.72 — 0.04	Marked spherocytosis
8/17/ "	3.64	67	8	0.72 — 0.22	Marked spherocytosis
9/ 6/ "	4.19	77	4.5	0.80 — 0.28	Marked spherocytosis
10/15/ "	2.89	58	6	0.64 — 0.04	
11/24/ "	1.24	24	12.5	0.68 — 0.04	Many nucleated red cells and spherocytosis
11/28/ "	2.24	40	10.5	0.72 — 0.24	
12/11/ "	2.03	42	8	0.72 — 0.24	
12/19/ "	1.51	28	16	0.68 — 0.26	
1/22/1940	2.29	46	10	0.68 — 0.24	Improvement due to repeated transfusions
2/16/ "	3.41	68	2.6	—	
2/29/ "			*Salpingo-oöphorectomy*		
3/ 8/ "	2.50	47	5.6	0.68 — 0.16	Spherocytosis
3/15/ "	2.94	60	17	0.64 — 0.04	Many nucleated red cells and spherocytes
4/12/ "	4.31	76	2.6	0.60 — 0.12	
5/10/ "	5.04	101	1.7	0.52 — 0.12	Spherocytes very rare
6/28/ "	5.52	102	0.9	0.50 — 0.16	Spherocytes very rare
7/ 5/ "	5.38	102	2	0.46 — 0.12	No spherocytes
8/ 7/ "	4.98	96	2.7	0.44 — 0.12	No spherocytes
6/30/41	5.04	95	1.0	0.42 — 0.12	Red cells normal

A somewhat similar case is reported by Suarez and Etcheverry (1937).[35] In this instance a dermoid cyst arising from the splenic hilus was discovered. Splenectomy, together with removal of the tumor, was performed but the patient unfortunately died shortly after operation. Definite relationship of the tumor to the hemolytic anemia was thus not established.

The coexistence of a dermoid cyst and hemolytic anemia does not necessarily indicate an etiologic relationship. This is illustrated by an observation of Watson.[38a] In this case, that of a 19 year old girl, hemolytic anemia in association with a large ovarian cyst was present. The laboratory findings were as follows: Hemoglobin 32 per cent, red blood cells 1.15 million; white blood cells 6000, reticulocytes 15 per cent, hypotonic fragility normal, icterus index 42, "indirect" bilirubinemia. The anemia was of the macrocytic variety. The daily fecal urobilinogen excretion was 1106 mg., indicative of a severe hemolytic process. Marked auto-agglutination of the red cells was observed. Oöphorectomy was performed without result, but when splenec-

tomy was then done, there was a very slow, steady improvement which finally led to complete recovery. This observation indicates that a dermoid cyst is not necessarily in and of itself the entire cause of a hemolytic process, but that it might have a definite relationship nevertheless. It is possible that these cases may require removal of both the tumor and the spleen.

Case 2. Lymphosarcoma arising within the pancreas. A. R., a 50-year-old Jewish merchant with a completely negative past history, complained of fever of several weeks' duration, dyspnea, and progressive weakness. During the two weeks prior to admission to the hospital he had noticed slight jaundice, together with severe and cramp-like mid-abdominal pain radiating to the left costovertebral region. Examination showed an emaciated man with a yellowish tint of the skin and sclerae. Neither the liver nor spleen was palpable. There was distinct tenderness in the left costovertebral region. The laboratory data were as follows: urine negative for albumin, sediment normal, no bilirubin, greatly increased quantity of urobilinogen; blood—hemoglobin 40 per cent, red blood cells 1.9 million, white blood cells 22,000, reticulocytes 28 per cent; anisocytosis, poikilocytosis and marked spherocytosis; hypotonic fragility 0.60–0.28 per cent; differential count of the leukocytes, marked "shift to the left." The icterus index was 40, and the bilirubinemia was of the indirect variety. Roentgen-rays of the kidneys were normal, but a gastrointestinal series showed an indentation along the posterior wall of the stomach, due probably to an extrinsic mass. Laparotomy was performed, and a tumor the size of a lemon arising from the middle third of the pancreas was found. The tumor, which was separated from the pancreas by a thick capsule, was completely removed. Unfortunately the patient died 24 hours after operation. Sections of the tumor showed a "round cell" (lympho-) sarcoma with areas of necrosis.*

Although no definite proof is present regarding the symptomatic character of the hemolytic anemia in this case, the completely negative family history and the simultaneous development of the hemolytic process with the symptoms of the neoplasm are in favor of this view. Similar observations have been made by Thompson [36a, 36b]: hemolytic anemia in three cases of sarcoma of the spleen; Waugh [39]: hemolytic anemia with increased hypotonic fragility in two cases of carcinoma with metastasis to the bone-marrow; and Caroli and Lavergne [6]: acute hemolytic anemia with metastatic bone marrow involvement from primary carcinoma of the stomach.

Although the reports of hemolytic anemia in association with malignant neoplasms are few in comparison with the great frequency of these disorders, it is possible that this is due in part at least to the relatively little attention which is paid to the type of anemia in a given case of malignancy. In other words, anemia if present is said to be "secondary," and given scant attention. The mechanism responsible for the sudden development of the hemolytic process in a case of neoplastic disease is at present obscure, although the possibility is present that some sort of hemolysin is produced (*vide infra*).

II. Hemolytic anemia in Hodgkin's disease. The usual type of anemia found in cases of Hodgkin's disease is of the hypochromic variety; it is usually mild, and of great severity only in the terminal phases of the disease.

* This case was seen by one of us (K. S.) in Vienna in 1934. A complete histological description of the tumor is unfortunately not available.

Occasionally, due to invasion of the marrow, a normocytic anemia may be seen. Rarely, hemolytic anemia may be present, as in the case reported below.

Case 3. M. L., a 45-year-old woman, had developed cervical adenitis 18 years previously. At biopsy the diagnosis of tuberculosis was made. Six years prior to the present illness a mediastinal tumor was discovered and treated with roentgen-rays. Three months before admission to the hospital the patient developed fever, slight jaundice, weakness, dyspnea on exertion, and increasing pallor. Examination showed slight jaundice and a readily palpable spleen. There was no peripheral lymphadenopathy but a large mediastinal mass was found on roentgen-ray examination of the chest. The laboratory data were as follows: urine, no bilirubin, urobilinogen greatly increased; blood, hemoglobin 52 per cent, red blood cells 1.8 million, white blood cells 12,600, reticulocytes 12.6 per cent. There was marked anisocytosis, poikilocytosis and spherocytosis. The hypotonic fragility was 0.60–0.35 per cent, but the lysolecithin fragility was normal on two occasions. Examination of the relatives (mother and two children of the patient) was completely negative for the presence of hemolytic jaundice. The diagnosis of symptomatic hemolytic anemia was made and splenectomy advised despite the presence of Hodgkin's disease. Operation revealed the typical "porphyric" spleen of the disease. Following operation there was improvement in the anemia, which then became hypochromic: hemoglobin 50 per cent; red blood cells 3.5 million; color index 0.7. The patient felt much better for about five months, following which large masses of cervical lymph nodes appeared, and shortly afterwards the patient died. Postmortem examination was not obtained.

The occurrence of hemolytic anemia in Hodgkin's disease has been repeatedly observed. The first case was described by Holler and Paschkis (1927) [19] who splenectomized a patient with hemolytic anemia without any clinical evidence of Hodgkin's disease, but found to their surprise a porphyric spleen. Singer (1936) [34c] described a case and summarized 13 cases from the literature. Other cases not described in Singer's article are those of Kwaszewska,[25] Watson (three cases),[38a] Schiapolli,[32] Bruins Slot,[5] and v. Braitenberg.[4] The spleen was involved in almost all of the cases, and in some (Holler and Paschkis,[19] Gripwall,[14a, b] Singer [34c]) splenectomy led to a temporary improvement with complete disappearance of the hemolytic anemia which was later replaced by a hypochromic microcytic anemia. The almost constant involvement of the spleen together with the effect of splenectomy in some of the cases suggests that a primary splenic disorder may be responsible for the development of the hemolytic process. Against this interpretation is an observation by v. Braitenberg [4] in whose case the spleen showed none of the pathological lesions of Hodgkin's disease. Davidson,[8b] Parkes Weber and E. Schwarz,[28] Watson [38a] and others have pointed out that the anemia in these cases is of the macrocytic variety. Dameshek and Schwartz [7a] believe, however, that the macrocytosis is more apparent than real ("pseudo-macrocytic"). They are of the opinion that the macrocytosis of certain cases of hemolytic anemia is due to the presence of numerous reticulocytes, which are much larger than the mature orthochromatic red cells. The hypotonic fragility of the erythrocytes in most of the cases was increased but in some cases was normal (Gripwall,[14b, 14c] Bensis and Gout-

tas [2]). Again, the mechanism resulting in the development of the hemolytic process is obscure.

III. Hemolytic anemia in leukemia. Anemia is a very common finding in chronic lymphatic and myelogenous leukemia. Usually it is normocytic and due to replacement of the erythropoietic tissue in the bone marrow by the proliferating process. Occasionally, however, a typical hemolytic syndrome with jaundice, spherocytosis and increased hypotonic fragility may be present. We have observed two such cases.

Case 4. F. C., a 70-year-old man, was admitted to the hospital October 27, 1938 in a semicomatose condition. The history as obtained from a daughter revealed that the patient had been healthy until five years previously when mild diabetes was discovered. On the day before entry he was apparently well and without jaundice. The following day his son noted that he walked with a heavy shuffling gait, and that he looked weak and yellowish. He complained of weakness and nausea. Immediately prior to admission to the hospital he was quite rational; he shortly became extremely weak, suddenly became semicomatose and began to vomit. Examination revealed an elderly, moribund man with marked pallor and moderate jaundice; the liver and spleen were readily palpable. One large lymph node in the right axilla and several small inguinal nodes were felt. The laboratory findings were as follows: hemoglobin 36 per cent; red blood cells 2.4 million; white blood cells 105,000 (!). The platelets were abundant. The smear showed extreme lymphocytosis (polymorphonuclear neutrophiles 8, lymphocytes 92, monocytes 0), the lymphocytes being almost all of the mature variety. The red cells showed very marked spherocytosis which was well brought out in the fresh preparations. The hypotonic fragility was 0.72–0.28 per cent, with a normal lysolecithin fragility. The reticulocytes numbered 8.3 per cent. An occasional nucleated red cell was seen. The bilirubin content of blood was 4.2 mg. per 100 c.c., with an indirect van den Bergh reaction. The urine contained albumin and sugar, but no bilirubin, and the urobilinogen content was 1:80. The blood sugar was 482 mg. per cent, the non-protein nitrogen 78 mg. per cent, and the CO_2 combining power 31.8 volumes per cent. A diagnosis of chronic lymphatic leukemia, acute hemolytic anemia, and diabetic coma was made. Despite treatment with insulin and two blood transfusions, the patient died the same day. At postmortem examination the liver weighed 2490 gm. and showed histologically large accumulations of mature lymphocytes in the portal areas without a corresponding increase in the periportal connective tissue. The spleen, which weighed 620 gm., showed large masses of mature lymphocytes in the pulp with complete effacement of the normal splenic architecture. There was generalized enlargement of lymph nodes, particularly marked in the mesentery. Microscopic examination revealed massive lymphocytic infiltration and proliferation in the pulp and sinuses with some infiltration of the connective tissue capsule and the adjacent fat. The bone marrow was pinkish gray, very hyperplastic, and greatly infiltrated with lymphocytes. Slight normoblastic hyperplasia was noted.

Case 5. Louis F., a 57-year-old Jewish photographer, noticed "lumps" in his neck and a mass in the left upper part of his abdomen approximately 8 to 10 years before admission to the Pratt Diagnostic Hospital on November 15, 1940. About a year prior to admission a physician found generalized lymphadenopathy, well-marked splenomegaly, a leukocyte count of 200,000 per cu. mm. with 99 per cent lymphocytes. He was referred to the Tumor Clinic of the Boston Dispensary for treatment and in March, 1940 was given four roentgen-ray treatments of 25R each to the entire body ("spray"). Although the hematological response was quite satisfactory, the leukocyte count dropping from 367,000 to 14,000, the patient developed a severe reaction in the form of weakness, fatigue, anorexia, vomiting, and marked loss in weight.

From that time on the course was unsatisfactory. A month later, in April, 1940, a generalized eruption resembling varicella appeared; histologically, the lesions were typically leukemic. The leukocyte count gradually rose to over 200,000 and on October 5 and 8, 1940 he was given two roentgen-ray treatments of 150R each over the spleen. He complained of vomiting and diarrhea, and intermittent jaundice gradually became apparent. He rapidly became weaker and paler, although there was some regression in the size of his lymph nodes and spleen. Within a period of five weeks or less, the red cell count dropped from 3.04 million to 1.71 million. There was then slight improvement, but in the two weeks prior to admission to the hospital, the red count rapidly fell from 2.54 million to 0.86 million.

Examination on admission November 15, 1940 revealed a very thin, pale, slightly icteric man. The temperature was 101° F., the pulse 100 per minute. There was generalized lymphadenopathy, the glands being firm, discrete, and measuring 3 to 8 cm. in length. The spleen was felt 15 cm. below the left costal margin, and the liver was felt 10 cm. below the right costal margin.

The laboratory data were as follows: Urine: slight trace of albumin; no bilirubin; urobilinogen greatly increased; Stools: dark color; daily fecal urobilinogen output (four day sample) 225 mg. per day, approximately five times normal for the red count; Blood: Hemoglobin 24 per cent; red blood cells 0.86 million; hematocrit 12 per cent; M. C. V. approximately 130 c. micra; white blood cells 155,000; Differential Count: polymorphonuclear neutrophiles 3 per cent, lymphocytes 93 per cent, monocytes 4 per cent. Platelets 93,000. Reticulocytes 33 per cent. The blood picture was "pseudo-macrocytic" in type, i.e., the large numbers of reticulocytes present resulted in apparent macrocytosis. Careful examination of the mature erythrocytes, however, disclosed that they were for the most part smaller than normal and that many spherocytes were present. The hypotonic saline fragility was .52 per cent beginning hemolysis and .28 per cent complete hemolysis (control .44–.24 per cent). The lysolecithin fragility was normal. The serum bilirubin was 9 mg. per 100 c.c., and of the indirect variety.

Three transfusions of 500 c.c. of blood were given with slight improvement. On December 5, hemoglobin was 40 per cent, red cell count 1.62 million, reticulocytes 33 per cent, platelets 32,400, leukocyte count 75,000 (lymphocytes 94 per cent). There were fewer spherocytes. The question of splenectomy was discussed, but the idea was quickly abandoned in view of the marked involvement of the bone marrow with lymphoid tissue as determined from sternal puncture and trephine biopsies.

The possibility that the roentgen-ray treatments directed over the spleen were in some measure responsible for the development of the hemolytic anemia in this case of chronic lymphatic leukemia must be considered. Certain it is that prior to the roentgen-ray treatments, the patient was in moderately good condition; directly following the first series (spray therapy), he felt poorly, lost considerable weight, and developed a leukemic rash. Following the second series which was given over the spleen, he developed hemolytic anemia.

The occurrence of a well-defined hemolytic syndrome in chronic lymphatic or myelogenous leukemia is rare, although it has been repeatedly observed (cases have been reported by Haden,[15c] Paschkis,[29] Watson,[38a] Marchall, Dany and Grupper,[26] Troisier and Tixier,[37] Klima,[22] and Singer.[34a] In Haden's case, splenectomy was performed on the assumption that an idiopathic process was present. The hemolytic process continued unabated and

six months later the typical features of chronic lymphatic leukemia became evident.

Rhoads [80] has recently emphasized a hemolytic component which he states is frequent in "refractory" or "aplastic" anemia. Included in this rather heterogeneous group with a common denominator of severe normocytic anemia, leukopenia, and thrombocytopenia are a number of cases of aleukemic leukemia and atypical or generalized Hodgkin's disease. We have recently observed two such cases in which mild icterus and increased fecal urobilinogen output were present in addition to the severe anemia.

In one (R. F.), chronic aleukemic myelogenous leukemia was present with the following blood counts: hemoglobin 42 per cent (6.5 gm.); red blood cells 2.25 million; white blood cells 3400; platelets 657,000; reticulocytes 3.0 per cent; polymorphonuclear neutrophiles 35 per cent, lymphocytes 61 per cent, monocytes 1 per cent, eosinophiles 3 per cent. The hypotonic fragility was .48–.20 per cent. Blood bilirubin was 1.6 mg. per 100 c.c. (indirect reaction), icterus index 12 units, and daily fecal urobilinogen output 223 mg. (about two to three times the normal value for the patient's red cell count).

In another case (O. H.), with aleukemic reticulosis, the following blood counts were present: hemoglobin 46 per cent; red blood cells 2.52 million; white blood cells 4300; platelets 277,000; reticulocytes 3.3 per cent. On January 3, 1941, there was no appreciable icterus but the blood bilirubin was 1.7 mg. From January 16 to January 25, the patient received seven "spray" roentgen-ray treatments of 25R each. On February 3, the sclerae were definitely icteric and the blood bilirubin content was 1.5 mg. Studies of the fecal urobilinogen were not done.

Watson [38a] has emphasized the macrocytic character of the hemolytic anemia in leukemia. In our first case there was marked spherocytosis without macrocytosis; in the second case, spherocytosis was not a striking phenomenon, although it became readily evident when the rate of hemolysis became greatly increased. Before this was apparent, the anemia was superficially macrocytic, although careful analysis of the cell diameters of both the reticulocytes and non-reticulocytes demonstrated the "pseudo-macrocytic" character of the anemia.

Possibly related to the cases of hemolytic anemia in leukemia are those in association with Boeck's sarcoid and giant follicle lymphoma. Haden [15c] has described an interesting case of hemolytic anemia in which a probable sarcoid involving both lungs was present. The spleen was not enlarged. Roentgen-radiation of the pulmonary process resulted in disappearance of both the sarcoid and the hemolytic process. Haden [15a, b] stated that although the exact cause of the hemolysis was not clear, it was probably due to some toxin incidental to the primary disease in the lung. At the Mt. Sinai Hospital (N. Y.) * a case was recently observed in which there was generalized lymphadenopathy, extreme splenomegaly, and hemolytic anemia. Biopsy of one of the nodes demonstrated giant follicle lymphoma. Following roentgen-ray therapy to the spleen and lymph nodes, there was definite im-

* Personal communication from Dr. Louis R. Wasserman, who will report this case in detail.

provement in the anemia and jaundice and diminution in the output of urobilinogen.

That the hemolytic process in all of these cases was in some manner dependent upon the abnormality of lymphoid apparatus is quite clear, although the exact mechanism for the destruction of the red cells is quite obscure (see below).

V. Hemolytic anemia in liver disease. In recent years increasing attention has been paid to the anemia associated with hepatic disorders. Except when hemorrhage or a complicating infection are present, the anemia is either normo- or macrocytic (Wintrobe,[42a, b] Wright,[43] Rosenberg [31] and others). Eppinger,[10] Fellinger and Klima,[11] and Watson [38a, b] have emphasized the hemolytic character of this anemia as indicated by an increased output of fecal urobilinogen. There is frequently a rough parallelism between the severity of the anemia and the degree of liver damage. The blood picture resembles that of pernicious anemia more closely than it does that of hemolytic jaundice. Spherocytosis is not usually observed and the saline fragility is usually normal. Fullerton and Davidson,[8a] however, report a case of macrocytic anemia in association with cirrhosis of the liver in which the hypotonic fragility was abnormal (starting at 0.7 per cent of NaCl), and Watson [38a] concedes that the mean cell thickness of the red cells may be increased even in the presence of macrocytosis. From these and other data it may be concluded that the anemia of liver disease, although occasionally of hemolytic character, differs usually in many respects from the picture of symptomatic hemolytic jaundice as discussed in this paper. The following case demonstrates the occurrence of such a symptomatic hemolytic syndrome in liver disease.

Case 6. E. D. G., a 25-year-old housewife, was admitted to the J. H. Pratt Diagnostic Hospital on April 26, 1941, with the complaint of progressive anemia, jaundice, and weakness of about 3 years' duration. In May 1938, she had been delivered of twins; the pregnancy and childbirth were both uncomplicated, but shortly after delivery she became increasingly pale and weak. About 8 months after delivery her family physician treated her for anemia with large doses of iron and injections of liver extract. Since no relief ensued, she was hospitalized and given six transfusions of blood. There was only temporary relief and for the following two years she was studied and treated by various physicians and hospitals but continued to feel weak and dyspneic. Just prior to her first visit to the Blood Clinic of the Boston Dispensary, April 2, 1941, the diagnosis of Hodgkin's disease of the spleen had been made at another hospital and roentgen-ray therapy over the spleen had been given, also without relief. Following the roentgen-ray treatments which caused severe nausea and vomiting, there occurred a rather rapid increase in symptoms and the red cell count, which was 1.71 M. per cu. mm. on April 2, had declined to 1.06 M. on April 29. The remainder of the history was irrelevant; there was no family history of jaundice, anemia, or splenomegaly. Alcoholism was denied.

Physical examination on admission showed marked pallor, slight icterus, a normal appearing tongue, slight enlargement of the heart with a soft systolic murmur, an enlarged liver palpable 2 fingers' breadth below the right costal margin and a greatly enlarged spleen extending to the umbilicus. The blood findings were as follows: Hgb.

27 per cent (4.2 gm.); RBC 1.06 M.; color index 1.3; WBC 2900; platelets 81,000; polymorphonuclear granulocytes 49 per cent (4 band forms); lymphocytes 26 per cent; monocytes 12 per cent, eosinophiles 12 per cent, basophiles 1 per cent. The mean corpuscular volume varied from 130 to 150 cu. micra, the mean cell diameter was 8.5 micra (normal 7.5 micra), the mean cell thickness was 2.7 micra (2.2 micra high normal). The reticulocytes averaged 8.8 micra in diameter, and the mature orthochromatic red cells 8.2 micra. The reticulocytes varied between 19.5 per cent (April 2) and 49.5 per cent (May 1). The red cells showed marked changes in size, shape, and staining characteristics with polychromatophilic macrocytes outstanding. There was no spherocytosis. The hypotonic fragility test showed beginning hemolysis at 0.42 per cent of NaCl, and complete hemolysis at 0.20 per cent. The Ham acid fragility test was negative. The mechanical fragility of the red cells (Dameshek and Miller [7d]) was definitely abnormal, 27 to 33 per cent hemolysis occurring after 3 hours of mechanical shaking with glass beads (normal value 5 to 7 per cent hemolysis).

The urine showed no bilirubin but contained greatly increased quantities of urobilinogen. The daily fecal urobilinogen output (average of 4 days output) was 1925 mg., approximately 25 times the normal value. The blood bilirubin was of the indirect type and measured 3.0 mg. per 100 c.c.

The gastric analysis showed the presence of free HCl. Roentgen-rays of the chest and long bones were negative. The sternal puncture showed extreme normoblastic hyperplasia, with a marked relative reduction in the leukocytes and megakaryocytes. The bilirubin excretion test (50 mg. of bilirubin injected intravenously) showed 100 per cent retention of the dye, indicating definite hepatic damage. Tests of the serum for isohemolysins, autoagglutinins, and autohemolysins were negative.

Thus the various studies showed the presence of a severe, truly macrocytic anemia, leukopenia, thrombopenia, but a very marked reticulocytosis. The bone-marrow showed extreme erythroblastic hyperplasia and the fecal urobilinogen output indicated an unusually marked hemolytic process. Although the complete retention of the injected bilirubin pointed towards definite hepatic dysfunction, the significance of this observation was at first not appreciated. The patient was given three transfusions of blood from compatible donors and was then transferred to the Beth Israel Hospital for splenectomy. This, together with biopsy of the liver, was performed by Dr. W. S. Levenson on May 13, 1941. The liver was grossly nodular and irregularly mottled in appearance. The spleen was extremely large, weighing 1960 gm. Histologically the liver showed a moderate amount of fibrous tissue within the portal areas and also thin bands of young fibrous tissue extending from the portal area to within the lobules in a fan-like fashion. In both types of fibrous tissue a moderately heavy sprinkling of inflammatory cells consisting mainly of lymphocytes and eosinophilic leukocytes was demonstrable. No evidence of abnormal hematopoiesis was present. Diagnosis: subacute hepatitis. The spleen showed histologically a marked diminution of lymphocytes within the pulp, some giant cells probably of reticulum cell origin, and hematopoietic activity which appeared to be limited to the cells of the granulocytic series.

The patient made a complete uneventful recovery. Without further transfusions, there was an almost immediate increase in Hgb. and red cell count and a concomitant decrease in bilirubin and reticulocytes. On May 20, Hgb. was 46 per cent; RBC 2.17 M; reticulocytes 4.2 per cent and serum bilirubin 0.6 mg. On June 9, Hbg. was 57 per cent, RBC 3.32 M; WBC 8000; reticulocytes 3 per cent; platelets approximately 1.5 M, and serum bilirubin 0.6 mg. On July 14, the Hgb. had risen to 74 per cent and the red cell count to 3.5 M. The MCV. and MCD. remained elevated, however, at 109 cu. micra and 8.3 micra respectively, indicating persistent macrocytosis. The hypotonic fragility was 0.40 to 0.04 per cent.

The persistence of moderate anemia in association with macrocytosis and the finding of severe liver disease indicated that the residual macrocytic anemia was on

the basis of hepatic disease. However, the hemolytic component was now completely absent, as evidenced by the return to normal values of the blood bilirubin, the reticulocytes, and the fecal urobilinogen output. This indicated that although the hemolytic process was secondary or symptomatic of the hepatic disease, it was nevertheless primarily splenic in origin. Something abnormal within the spleen had resulted in increased blood breakdown, which could only be relieved by splenectomy.

VI. Hemolytic anemia in infectious diseases. Hemolytic anemia is occasionally observed in the course of various infectious diseases. Widal, Abrami and Brulé [41] listed malaria, streptococcic and staphylococcic infection, tuberculosis, anaerobic organisms including *B. Welchii*, and ankylostomiasis as possible causes. That toxic substances of non-bacterial origin may also produce hemolytic anemia has become generally known from observations of the untoward sequelae occurring with sulfanilamide administration (Kohn,[24] Harvey and Janeway,[17] and others). The same effect may be produced by lead (Davidson,[8b] Aub, Fairhall, Minot and Reznikoff [1]), phenylhydrazin (Kaminer and Rohnstein [21]), etc. Strictly speaking, these "drug anemias," although they often present spherocytosis, etc. (c.f. Dameshek and Schwartz [7a]), do not belong in the group of symptomatic hemolytic anemias as defined in this paper. The symptomatic hemolytic anemias of infectious diseases disappear if the underlying disease is successfully treated, thus again demonstrating a causal relationship. This was observed in the following case.

Case 7. M. L.,* a 62-year-old man, developed an acute febrile illness and on admission to the hospital four days later was found to have complete consolidation of the left lower lung. The temperature was 105° F., the pulse 120, and the respirations 40 per minute. Slight jaundice and marked pallor were also noted. The laboratory findings were as follows: hemoglobin 41 per cent; red blood cells 1.2 million; white blood cells 38,900. The blood smears showed moderate spherocytosis, and many nucleated red cells. The hypotonic fragility was 0.54–0.42. The urine showed slight albuminuria but no bile. The total protein of the blood was 6.7 gm. per cent. The sputum showed a type 17 pneumococcus. Serum bilirubin was indirect and measured 4.6 mg. per 100 c.c. The unusual feature of the case was the presence of a very strong panagglutinin in the blood. It was at first impossible to perform red cell counts because of marked agglutination in the pipettes. The erythrocytes of 36 successive donors were agglutinated by the serum of the patient. Dilution of the serum was without effect. Finally, compatability tests were performed by incubating the blood at body temperature, following which the patient was transfused without incident. Treatment with sulfapyridine and specific Type XVII antipneumococcic serum was instituted. The panagglutinin gradually diminished in intensity. With subsidence of the pneumonic process, there was a gradual rise in the red cell count to 3.0 million, hemoglobin to 53 per cent. With complete recovery, the autoagglutinin disappeared entirely and the blood levels became normal.

It is possible that the hemolytic anemia in this case was induced by intravascular agglutination resulting from the activity of the autoagglutinin. Another possible interpretation is that the autoagglutinin indicated the pres-

* This case is reported through the kindness of Dr. Joseph E. Porter and Dr. Mortimer C. Warren of Portland, Maine.

ence of an associated hemolysin. Hemolytic substances of the immune body type have recently been described by Dameshek and Schwartz [7a, b] in acquired hemolytic anemia of the idiopathic type. Whether the present case was one of acute idiopathic hemolytic anemia with accompanying pneumonia or whether the pneumonia was responsible for the hemolytic anemia is not clear. Since both processes began and disappeared simultaneously the latter relationship seems probable.

Symptomatic hemolytic anemia in association with a tuberculous process of the spleen has recently been described by Engelbreth-Holm.[9] In tuberculosis of the spleen the anemia is usually normochromic to hyperchromic (Howells [20]), but in Engelbreth-Holm's [9] case the anemia was typically spherocytic: hemoglobin 45 per cent; red blood cells 2.0 million; color index 1.15; vol. index 1.17; reticulocytes 37 per cent; leukocytes 16,700; hypotonic fragility 0.80–0.04; icterus index 20. Splenectomy was performed, but the patient died of thrombosis of the inferior vena cava. There was no evidence of congenital or familial jaundice. Thompson [36a] also reports a case of "atypical hemolytic anemia" with caseous tuberculosis of the spleen and lymph nodes. Giffin [13] (1919) described two cases of primary tuberculosis of the spleen with hemolytic jaundice. There was no evidence of familial hemolytic disease. In one, the hypotonic fragility was increased. Splenectomy was performed in both and was followed by complete recovery. Although Engelbreth-Holm does not relate the hemolytic anemia to the tuberculous involvement of the spleen, Giffin [13] discusses this possibility, and indeed such a relationship seems quite possible.

Discussion

1. Diagnosis and Differential Diagnosis. The diagnosis of symptomatic hemolytic anemia may be very difficult, especially since the syndrome is not at present well-known. Diagnosis of the hemolytic component (i.e., increased blood destruction) should at least be suspected from the presence of jaundice in association with pallor, and in the absence of bile from the urine. The spleen is furthermore palpable in most cases. Further study will reveal bilirubinemia with an indirect van den Bergh reaction, normal or dark-colored feces with greatly increased output of urobilinogen, and usually an increase in the urinary urobilinogen. Spherocytosis, if carefully looked for, should be recognizable in most cases in both fresh and stained preparations. The contrast in appearance between these small, dense-appearing cells and the large reticulocytes is striking. All the evidences of increased regenerative activity on the part of the marrow are also present, i.e., reticulocytosis, polychromatophilia, nucleated red cells, polymorphonuclear leukocytosis, immature granulocytes, and thrombocytosis. The bone marrow itself (sternal puncture) shows extreme hyperplasia, particularly of the erythroblastic elements. When the definite diagnosis of a hemolytic process has been made,

the case must be further analyzed. The hemolytic processes may be subdivided into three large groups:

First pernicious anemia must be considered. In this condition there is a true macrocytic anemia, the mature orthochromatic red cells being larger on the average than normally. This is quite in contrast with the "pseudomacrocytic" hemolytic processes in which the only large erythrocytes are the immature polychromatophilic reticulocytes. Gastric analysis reveals complete achlorhydria with histamine, whereas our hemolytic cases tested showed the presence of free HCl. The sternal puncture in pernicious anemia reveals a characteristic megaloblastic hyperplasia with the presence of bizarre giant metamyelocytes. There is, furthermore, the therapeutic test with liver extract, which, by the way, has usually been performed before the hematological consultant sees the case. With all these criteria in mind, the differential diagnosis between the "liver extract" deficiency state known as pernicious anemia and hemolytic anemia is usually not a very difficult procedure.

The second group comprises a heterogeneous group of hemolytic syndromes including the congenital and acquired idiopathic hemolytic anemias, and such conditions as sickle-cell anemia, Cooley's erythroblastic anemia, and the Marchiafava-Micheli syndrome of paroxysmal nocturnal hemoglobinuria. In the congenital condition, a careful familial history and hematological study of the family members may reveal other cases. It should be noted, as Dameshek and Schwartz [7a, b] have repeatedly stated, that spherocytosis and increased hypotonic fragility are by no means pathognomonic of the hereditary type, but are commonly seen in acquired cases. The lysolecithin fragility test (Singer [34a]) may be of aid in differentiating these two conditions, since the erythrocytes of the congenital type are more fragile to this lysin than those of the acquired variety. Isohemolysins and autoagglutinins should always be searched for since they are seen only in the acquired type.

Sickle cell anemia and Cooley's anemia should be readily diagnosed if the racial background, the presence of target cells (Haden and Evans,[15d] Dameshek [7c]), the reaction of the erythrocytes to incubation in the case of sickle cell anemia, the decreased saline fragility, and other factors (bone changes, etc.) are taken into account. The Marchiafava-Micheli syndrome is characterized by nocturnal hemoglobinuria and a chronic hemolytic anemia which according to Ham [16a] resides in a fundamental abnormality of the red blood cells. Spherocytosis is completely lacking and the hypotonic saline fragility is normal, although the "acid" fragility test (Ham) is positive. Splenectomy is furthermore completely without effect.

The third group consists of all hemolytic anemias of known etiology, i.e., those due to drugs, allergic reactions, as well as to various fundamental underlying conditions, i.e., symptomatic. The drug anemias may show an almost identical picture with acute hemolytic anemia, with complete subsidence upon cessation of the administration of the drug. Allergic hemolytic anemia is represented by favism, a condition which is apparently found

only in certain areas of Italy following contact with the fava bean plant. The mechanism of this condition is quite obscure. If all these conditions have been ruled out, the presence of symptomatic hemolytic anemia should then be considered, although ordinarily the situation presents itself in the reverse manner, i.e., the diagnosis of a hemolytic process has been made. Is it idiopathic or is it bound up with some underlying condition? This should always be searched for.

The diagnosis of the symptomatic form of hemolytic anemia is based first on the knowledge that this syndrome may occur in the presence of the several conditions as described in this paper and secondly on the symptomatology of the various underlying disorders. Hemolytic anemia which is symptomatic of Hodgkin's disease, lymphatic leukemia, lymphosarcoma, and giant follicle lymphoma, may be readily diagnosed in the presence of a relapsing fever (Pel-Ebstein type), lymphadenopathy, a characteristic blood picture, or the roentgen-ray findings of a mediastinal mass. However, when these indications are lacking, search should always be made in an apparently idiopathic hemolytic process for evidences of tumor, destructive bone lesions indicative of metastatic lesions, and invasion of the bone marrow. Thus in addition to a careful physical examination and roentgen-ray of the chest, roentgen-rays of the bones and sternal puncture are indicated in a hemolytic process to make reasonably certain that it is not "symptomatic." Even with all care, however, there will be occasional cases diagnosed as "idiopathic" which will eventually prove to be "symptomatic" in nature. This occurred in Case 1 (dermoid cyst of the ovary), and in Case 6 (severe liver disease). Haden [15b] also emphasizes this point in describing a case of what was apparently congenital or acquired hemolytic anemia but which failed to improve after splenectomy; chronic lymphatic leukemia was the final diagnosis. If a case of apparently "idiopathic" hemolytic anemia fails to respond or relapses after splenectomy, the possibility of an underlying disease which has been overlooked should be seriously considered and searched for. To summarize, the diagnosis of hemolytic anemia per se should now be made more frequently than in the past, especially when it is realized (*a*) that the designation of "secondary anemia" is meaningless; (*b*) that even slight icterus may be indicative of a hemolytic process. When the latter is discovered, appropriate measures must be taken to classify the hemolytic process as accurately as possible. In this way, the occasional case of hemolytic anemia due to an underlying disease will be recognized.

The prognosis of symptomatic hemolytic anemia depends on the underlying disease. If this disease is curable, the prognosis may be excellent. This is illustrated by Case 1 (dermoid cyst). Otherwise, the effect of splenectomy is by no means certain. There may be a temporary improvement in the hemolytic process, or even complete disappearance with a change to the more usual hypochromic type of anemia, or there may be no effect whatever. It is always advisable, if at all possible, to remove or ameliorate

the underlying disease before splenectomy is performed. As stated above, in order to effect a cure in a given case, it may be necessary to remove both a tumor such as a dermoid cyst and the spleen. These points, however, are not yet clear, and must await further observations.

2. Pathogenesis. The hematological picture of symptomatic hemolytic anemia is frequently identical with the "idiopathic" types—both inherited and acquired. This might indicate that similar pathogenetic mechanisms are at the basis of these disorders. A rough analogy with pernicious anemia may serve for illustration. In this disease, we have learned, chiefly through Castle's investigations, that the anemia develops if the physiological mechanisms of production, absorption or utilization of the antipernicious principle are disturbed by various pathological processes. In this way, the "symptomatic" types of pernicious anemia (i.e., those cases in which the fundamental abnormality was an organic lesion of the stomach or bowels) have become readily understood. Until the discovery of the efficacy of liver therapy, one of the few cases of pernicious anemia known to be permanently cured was associated with chronic ulceration of the small intestine (Seyderhelm [33]); upon resection of the lesions, the blood picture became permanently normal. Today the pathogenesis of this particular case of "symptomatic" pernicious anemia is interpreted as due to malabsorption of the anti-anemic principle. In hemolytic anemia, we may conclude by analogy that the pathogenesis of the symptomatic types may be explained on the basis of theories already extant concerning the "idiopathic" varieties.

Considerations regarding the pathogenesis of "idiopathic" hemolytic anemia are bound up with (1) the presence of spherocytosis and the associated increase in hypotonic saline fragility, and (2) the effect of splenectomy in the amelioration of this disorder. Although many different opinions are present regarding pathogenetic mechanisms, the outstanding ones are those postulating a faulty bone marrow, an increase in hemolysin production, or an abnormality of the spleen.

The theory of a faulty production of erythrocytes in the bone marrow was first proposed by Naegeli [27] who claimed that splenectomy did not alter the production of spherocytes by the marrow but simply removed the inhibitory effect of the spleen on the bone marrow. Following splenectomy, and despite the continued presence of spherocytosis, there is a return to a normal degree of blood destruction as measured by the fecal urobilinogen output (cf. Watson [38b, c]) or the pigment excretion may even become lower than normal. (Singer, Miller and Dameshek.[34d]) Various observers (Gripwall,[14] Ham and Castle [16b]) have on this account postulated that the spleen is the most important organ in this disease, the bone marrow simply producing abnormal red cells. The hemolysin theory [7a, b] on the other hand states that the shape of the red cells is altered outside the bone marrow by the action of hemolysins. Spherocytosis is interpreted as a precursor of hemolysis and the morphological expression of an alteration in the structure of the erythrocyte produced by various types of hemolytic substances.

In symptomatic hemolytic anemia, we must assume from the standpoint of the hemolysin theory, that the fundamental pathological lesion either itself produces or stimulates the production of hemolysins. If the hemolysin (or agglutinin) is of the immune body type, as in our case of pneumonia, it will occasionally be demonstrated. The demonstration of other types of hemolysins in these cases has thus far not been successful. Since various lesions of the spleen may be associated with the identical picture of symptomatic hemolytic anemia, one may suspect a direct stimulation of the spleen by these abnormal tissues. On the other hand, in the cases in which the hemolytic anemia is associated with an extrasplenic lesion (dermoid cyst for example) a more indirect process of stimulation must be assumed. The hemolysin theory, although in many respects highly hypothetical, offers at least some explanation of these obscure pathological conditions and may serve as a working hypothesis for further experimental investigations.

Ham and Castle [16b] have recently proposed another explanation for the hemolytic state, based in part on the work of Knisely [23] on the histology of the spleen, and in part on experimental observations with concanavalin-A, an agglutinating substance derived from the jack bean. According to these investigators, the combination of increased stasis (usually splenic) and agglutination is sufficient to explain the various types of hemolytic anemia. This explanation does not appear to have much significance in most of our cases of symptomatic hemolytic anemia, in which neither increased stasis nor agglutination (except in Case 6) were present. Recent experiments of Dameshek and Miller [7d] have tended to cast doubt on the importance of the factor of stasis while confirming the factor of damage to the red cell envelope by both hemolysins and agglutinins. It seems likely that substances which damage the red cell envelope develop occasionally in a number of different pathological conditions, and may result in "symptomatic" hemolytic anemia. These substances may frequently be of splenic origin. The spleen is probably not only a passive, mechanical organ of stasis, as stressed by Ham and Castle, but an active, cellular organ which may produce erythrocyte-injuring substances. As the result of the recent investigations of both groups of investigators, it seems likely the hemolytic syndromes are due to various etiological mechanisms involving hemolysins, agglutinins, complement activity, mechanical trauma, and constitutionally damaged red cells. We believe that certain disorders, notably lymphatic leukemia, lymphoid neoplasms, Hodgkin's disease and some infectious states occasionally result in hemolytic anemia by evoking one or more of these mechanisms.

Summary

A series of cases of acute hemolytic anemia occurring in conjunction with other diseases (dermoid cyst, chronic lymphatic leukemia, Hodgkin's disease, lymphosarcoma, severe liver disease, and pneumonia with a pan-

agglutinin) is described. These cases are classified as "symptomatic," a sub-group of the acquired hemolytic cases.

Spherocytosis and increased hypotonic fragility are often present in these cases, although a "pseudo-macrocytic" blood picture may be present. The presence of spherocytosis in these cases may indicate that this abnormality of the erythrocyte is due to certain as yet undefined hemolyzing agents.

The recognition of these cases is of distinct importance (*a*) in evaluating the type of anemia in certain cases of lymphomatous disease, and (*b*) in ruling out the presence of an "idiopathic" hemolytic process. Splenectomy may be valueless, but removal of the underlying process, such as a dermoid cyst, may be curative.

From the standpoint of pathogenesis, the recognition of these cases is further evidence in support of the hypothesis that hemolytic agents of various types, usually acting through the spleen, are responsible for the various types of hemolytic anemia. Certain disorders, notably lymphatic leukemia, lymphoid neoplasms, Hodgkin's disease, and some infectious states occasionally result in hemolytic anemia by evoking various types of etiological mechanisms.

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EXPERIMENTAL EXOPHTHALMOS AND ASSOCIATED MYOPATHY INDUCED BY THE THYROTROPIC HORMONE*

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THE term "malignant exophthalmos" designates the progressive and alarming proptosis which occurs in a small group, usually after thyroidectomy and in the presence of a low basal metabolic rate. Unless relieved by operative decompression of the bony orbit, as devised by Naffziger,[1] a high percentage of these patients develop corneal ulceration, infection, and fatal intracranial extension of the orbital cellulitis. The pathologic changes and immediate cause of the exophthalmos occurring in these patients were described in detail in previous reports.[1] In brief, the extraocular muscles were found to be enlarged from three to eight times. Grossly, the musculature of the orbital muscle cone was observed to be firm, pale and edematous. Various stages of degeneration were observed histologically with interstitial edema, proliferation of small round cells which tended to accumulate around blood vessels, and fibrosis which appeared more dense and extensive in the more advanced cases (figures 1, 2 and 3).

The fact that exophthalmos may occur with hyperthyroidism and yet may steadily progress to a malignant form in the presence of postoperative hypothyroidism suggests an indirect relationship with hormones affecting the thyroid gland, such as the thyrotropic hormone of the anterior pituitary body. A review of all cases of malignant exophthalmos in the University of California Hospital strongly suggested a glandular dysfunction in the majority of these patients, and in many instances the findings were consistent with some disturbance of the hypophysis. Because of the successes recently reported in the experimental production of exophthalmos by the use of whole extracts of the anterior pituitary body, the present studies were centered about this method.

A historical review of the older research and theories on exophthalmos,[1] as well as its experimental production with the use of extracts of the anterior pituitary body,[2] has been presented in detail previously and need not be repeated.

Although pathologic changes in the muscles were described in certain of these studies in which exophthalmos was produced experimentally by means of injections of the extracts of the anterior pituitary body,[3] it is by no means clear that the changes were primarily those of a myopathy, as is the case in the malignant exophthalmos of human beings. Furthermore, although the

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thyrotropic hormone in the extracts of the anterior lobe of the pituitary body was suspected as the factor responsible for the production of exophthalmos, conclusive evidence has not been obtained to substantiate this impression. The following experiments were undertaken to clarify these points.

Methods

The extracts of the anterior pituitary body used in these studies were:

1. An alkaline extract of the whole pituitary body as prepared by Parke, Davis and Co.*
2. An alkaline extract of the whole pituitary body as prepared by E. R. Squibb and Sons.*
3. A thyrotropic extract prepared according to the method of Junkmann, by Uyei † of the Institute of Experimental Biology of the University of California.
4. An adrenotropic extract prepared by Moon † according to the method described by Lyons.

Injections were made by the intraperitoneal route except in the case of the Junkmann preparation which was used subcutaneously. All injections were given daily over periods of from three and one-half to seven months, as indicated in each case.

Young male guinea pigs weighing between 200 and 400 grams were used in all tests. The animals were maintained on a diet of alfalfa and barley, with the addition of carrots once a week. Cauliflower leaves were substituted for this diet one day a week. The guinea pigs were weighed every two weeks, and measurements of their eyes were recorded weekly. Objective measurements of the eyes proved difficult. Direct methods were impractical, as they frightened the animals and resulted in struggling and sympathetic hyperactivity. Photographic methods were attempted, but the bright lights, essential for obtaining good pictures under identical lighting conditions, tended to make the guinea pigs close their eyes. The method that finally proved satisfactory was an optical system which utilized the principle of the camera lucida and, without disturbance to the animal, permitted indirect tracings of the eyes to be made quickly and accurately from a superior angle. The details of this method have been described previously.[2]

At the conclusion of each experiment the eyes and muscle cones of all guinea pigs were carefully dissected from the orbits, and the retrobulbar fat and tissues were examined. The eyeballs were measured and the extraocular muscles were fixed in a 10 per cent solution of formalin. Except in the initial group, in which the Parke, Davis preparation was used, each extraocular muscle was studied by two methods. One portion was stained by the

* Acknowledgment is made to Parke, Davis and Co. and E. R. Squibb and Sons for the extracts used in these studies.

† Drs. Uyei, Moon and Evans of the Institute of Experimental Biology of the University of California coöperated in preparing these extracts.

routine hematoxylin and eosin technic, the method used in the initial experiment referred to above, and the second by the Bodian method [4] for the nerve endings and the motor end-organs. The Bodian method also showed the muscle structure to good advantage and served as a check upon the hematoxylin and eosin preparations. In addition, specimens were taken from the right deltoid muscle of each pig as a control on the possibility that myopathy might have occurred elsewhere. These specimens were fixed in a 10 per

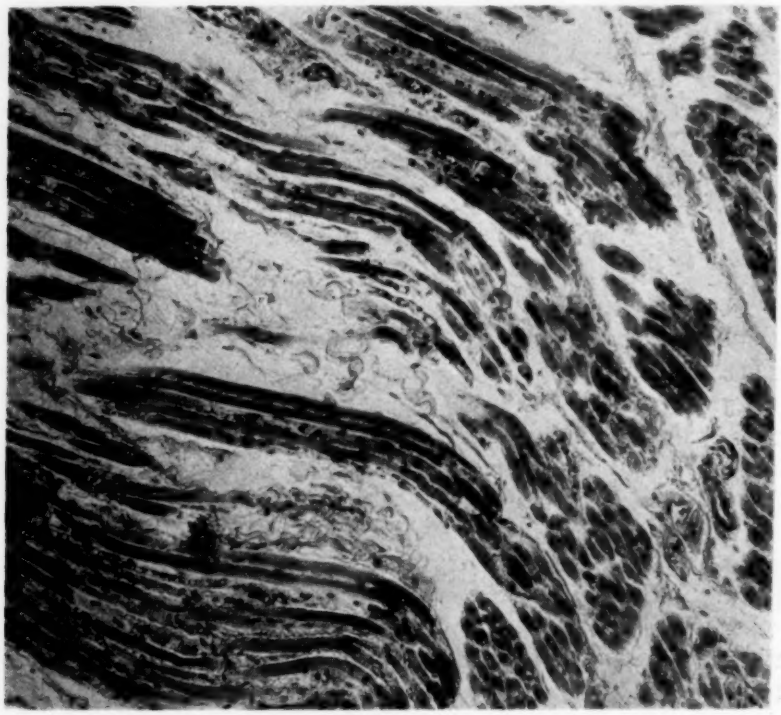

FIG. 1. Normal extra-ocular muscle of human being. H and E (× 105).

cent solution of formalin and were prepared for study by the usual hematoxylin and eosin staining technic.

In the initial experiment (Parke, Davis preparation) the thyroid glands were fixed in Zenker's solution and stained with hematoxylin and eosin. In the other experiments the pituitary, thyroid, and adrenal glands and the testes were removed from each animal, their sizes recorded, and sections of each fixed in Zenker's solution. In the final two experiments (adrenotropic and thyroidectomized control groups) the pituitary bodies were fixed in Flemming's solution and specially stained by Koneff of the Department of Anatomy of the University of California. The other glands were stained with hematoxylin and eosin. In addition, the adrenal glands were stained with Sudan IV and, in many instances, counterstained with methylene blue to determine the degree of lipid depletion present in each gland.

The kidneys of each animal were measured as a control on the variations of size normally occurring in individual organs. Sections of the kidney and liver were fixed in Zenker's solution, stained by routine hematoxylin and eosin methods, and studied for evidence of changes suggesting toxic effects.

FIG. 2. Myopathy of moderate degree in patient afflicted with malignant exophthalmos showing the interstitial edema and perivascular infiltration of small round cells. H and E (× 105).

RESULTS

1. Experimental exophthalmos produced by the whole extract of the anterior lobe of the pituitary body—Parke, Davis and Co. preparation. Eight of 12 male guinea pigs weighing approximately 400 grams each were injected daily by the peritoneal route with 1 c.c. of the alkaline extract of the whole pituitary body prepared by Parke, Davis and Co. The injections were continued over a period of seven months. Five guinea pigs of the group injected and the four controls survived the duration of the experiment.

In the animals injected a slight but definite exophthalmos appeared in approximately six weeks and slowly progressed throughout the period of administration of the extract. One or both eyes of all these guinea pigs became exophthalmic. The measurements of the eyes varied from 3.5 to 5 mm. as compared to a maximum reading of 3 mm. in the control group.

Toward the end of the experiment the average measurement in the control was slightly over 2.5 mm. Control studies indicated the method to be accurate to within 0.5 mm. Although the measurable exophthalmos was only from 0.5 to 2 mm., the constancy of these measurements and the accuracy of the methods made it certain that the phenomenon observed was real. Considering the incomplete bony orbits of guinea pigs and the size of these animals, it is evident that the changes were, in a relative sense, striking.

Except for one pig, whose exophthalmos was perhaps the greatest and most consistent throughout the whole period of injections, the weights of the

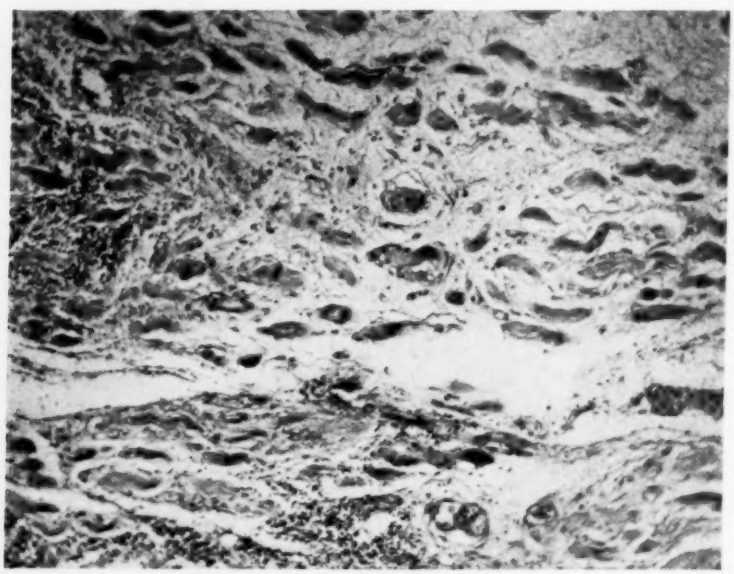

FIG. 3. Advanced myopathy in patient with malignant exophthalmos showing edema, the infiltration of small round cells, degenerative changes in the muscle fibers and fibrosis. H and E (× 105).

injected and control pigs were roughly comparable. The weight of the exceptional pig was under that of the others throughout the experiment and at the end was 780 grams as opposed to an average weight of 980 grams. The other guinea pigs varied in weight only 80 grams.

At the end of the seven months three guinea pigs of the injected group and two controls were killed and measurements of the eyes after death were recorded. Although their eyes were less prominent than during life, those of the injected animals were still from 1 to 1.5 mm. more prominent than those of the controls. The remaining two exophthalmic pigs and the controls were observed for another month, during which period no injections were given. The exophthalmos receded slightly in one guinea pig; in the other animal one eye (not exophthalmic) remained the same and the exophthalmos in the other eye was slightly accentuated. At the end of the eighth

month the postmortem measurements on the eyes of these guinea pigs likewise exceeded those of the controls. In this same connection it had been observed that ether anesthesia, although appreciably diminishing the exophthalmos, by no means abolished it.

The extraocular muscles of this group proved to be of interest. Grossly they appeared slightly larger in the animals injected than in the controls. Upon microscopic study the extraocular muscles of the injected guinea pigs

FIG. 4. Normal extra-ocular muscle of guinea pigs. H and E (× 120).

showed slight degenerative changes with interstitial edema, characterized by some loss of cross striations, an increased number of nuclei, which were smaller and more deeply stained than those of the controls, a tendency toward the separation of muscle fibers associated with poor alignment and suggestive breaking up of the fibers, and, finally, an increase in cellular debris. In addition, a process of cellular infiltration was observed, mostly of small round cells in clusters or "nests," but also of occasional polymorphonuclear cells. A wider variation in the size of the fibers was noted in the injected animals than was seen in the controls, and in those injected there was a tendency to the formation of giant fibers. The staining in the first group was correspondingly more irregular and unequal (figures 4 and 5).

The retrobulbar fat and tissues did not appear unusual in the injected animals. Slight edema of these tissues, as well as of the lacrimal glands, was observed occasionally, but this finding was not consistent nor did it correlate with the measured exophthalmos. The eyeballs were of the same size in both groups.

FIG. 5. Myopathy of moderate degree in the extra-ocular muscles of the guinea pig treated with the whole extract of the anterior lobe of the pituitary body. Note the cellular infiltration and the unequal staining, loss of cross-striation and poor alignment of the muscle fibers. H and E (× 120).

Although occasional thyroid glands of the injected guinea pigs showed changes compatible with a hypothyroid state of mild degree, in general these glands appeared to be within the limits of normal, as judged by the microscopic appearance of those of the control animals.

II. Experimental exophthalmos produced by the whole extract of the anterior pituitary body—E. R. Squibb and Sons preparation. Thirteen of 17 guinea pigs were given daily injections intraperitoneally of 0.5 c.c. of the alkaline extract of the whole pituitary body prepared by E. R. Squibb and Sons. Young male guinea pigs weighing between 250 and 350 grams were used. Their diet, care and follow-up studies were as previously indicated

under Methods. The outstanding feature in this experimental group, aside from the development of exophthalmos, was the curious clinical course. They underwent a severe reaction which, because of the manifestations of restlessness, hyperactivity, loss of weight and gross enlargement of the thyroid glands as seen at autopsy among those succumbing, was interpreted as having been caused by acute thyrotoxicosis. Of the 13 guinea pigs receiving injections, seven died between the ninth and twelfth days. One other died on the thirty-fifth day of injection. The condition of the five surviving guinea pigs of the test group gradually changed from an acute thyrotoxicosis to a normal or even slightly hypothyroid state. They became more quiet and put on weight slightly in excess of that occurring in the control group. These changes continued throughout the period of injection. Coincidental with the establishment of this refractory state, that is, from four to six weeks after the injections were begun, these animals showed objective evidence of exophthalmos in one or both eyes. The injections were continued over a period of five months, in three instances, and six months in the other two guinea pigs. The exophthalmos slowly progressed and, in most instances, tended to reach a peak at approximately the second month and again at the fifth. In one animal a gradual progression occurred through the entire five months and in another a plateau, attained by the third month, was exceeded only slightly at the end of six months of injections. If a maximum of 3 mm. is set for a normal reading (the average was 2.5 mm. in the control group), exophthalmos of from 0.5 to 1.5 mm., by measurement, occurred bilaterally in all of the guinea pigs injected. In seven of the 10 eyes the measurements were 4 mm. or more toward the end of the experiment. Although slight, the exophthalmos was within the limits of accuracy of the objective method used for measuring it, and the constancy of the results left no doubt as to the existence of this phenomenon.

Grossly the retrobulbar fat and tissues appeared to be within the limits of normal in this group, and the eyeballs of both injected and control animals were of the same size. As in the first experimental group, slight edema was noted in the retrobulbar tissues and lacrimal glands of occasional guinea pigs, but this observation was also made in one of the controls, and in general could not be correlated with the measured exophthalmos.

The microscopic appearance of the extraocular muscles was essentially the same as in the previous group (in which the Parke, Davis preparation was used), except that the picture was less well defined, the pseudohypertrophy was less apparent, the nuclei were fewer and paler, and the cellular infiltration was more questionable. The nerve endings and end-organs appeared to be normal.

Although at the beginning of the experiment the average weight of the guinea pigs in the control group slightly exceeded that of those to be injected, the reverse was true at the end. The difference in average weight was slight, however, and probably not significant. The adrenals, testes and

kidneys participated in this same slight variation of size, the organs of the injected animals being slightly larger than those of the control animals. In the gross, the thyroids of the injected group were considerably larger than those of the controls, larger than could be accounted for by the slight variation in size in the two groups. Microscopically, they appeared about the same as those of the control group. Myxedematous changes, if present, were slight, and the refractory stage which developed in the injected guinea pigs during this experiment could not, with certainty, be classified as a true hypothyroid state.

The adrenals showed changes suggestive of cortical stimulation. The cortical cells appeared slightly hyperplastic; the fat content, as judged by staining with Sudan IV and counterstaining with methylene blue, was increased; and diffuse hyperemia, which involved the zona reticularis in particular, was observed.

Except for testicular atrophy in one of the guinea pigs receiving injections, the testes appeared to be within the limits of normal. The pituitary bodies, kidneys, livers and right deltoid muscles likewise appeared to be normal.

III. Experimental exophthalmos produced by the thyrotropic factor (Junkmann preparation) of the anterior pituitary body. Eleven of 15 young male guinea pigs weighing between 250 and 350 grams were given daily subcutaneous injections of 0.2 c.c. of a 2 per cent solution of the thyrotropic hormone prepared by Uyei of the Institute of Experimental Biology of the University of California, according to the Junkmann method. The adjustment of the pH of the solution to 7.5–8 by the addition of a few drops of sodium hydroxide solution greatly facilitated the preparation of the solution used for injection. By biological assay 5 mg. of this solution was found to possess the potency of 100 thyrotropic units. The daily subcutaneous dose was therefore 80 thyrotropic units.

The course of the animals injected was of considerable interest in that it paralleled that of the group which received the alkaline extract of the whole anterior pituitary body supplied by E. R. Squibb and Sons. The test guinea pigs underwent a severe reaction which, because of its manifestations of restlessness, hyperactivity, loss of weight and gross enlargement of the thyroid gland seen at autopsy among those succumbing, was interpreted as an acute thyrotoxicosis. Of the 11 guinea pigs receiving injections three died on the eleventh or twelfth day and four others within a month. Three of the seven guinea pigs that died had one or both eyes clawed out. Four guinea pigs survived this stage and from an acute thyrotoxicosis gradually shifted to a condition characterized by signs directly the reverse of those described for the toxic state. They became quiet, tractable, and gained weight slightly in excess of that occurring in the control group. The average weight of the four surviving guinea pigs after five months of injection was 623 grams as compared with an average weight of 539 grams for the four

controls at the same time. This change is all the more striking because, initially, the control animals were, on the average, slightly heavier than the test group. These changes, interpreted as being hypothyroid in character, continued in spite of the daily injections of thyrotropic extract. Coincidentally with the onset of this hypothyroid state, that is, from four to six weeks after the injections were begun, these animals first showed evidence of exophthalmos. Injections were continued over a period of four or five months, when it was felt that the functional changes would have had time to project themselves in some permanent pathological pattern. The exophthalmos slowly progressed throughout this period and at the end the changes were so marked as to permit correct selection of the injected guinea pigs by casual inspection. By measurement the exophthalmos varied from 1 to 2.5 mm. in comparison with the eyes of the control animals. This group showed exophthalmos more consistently and to a more marked degree than either of the previous groups which received injections of the alkaline extracts of the whole anterior pituitary body. Correspondingly, the microscopic changes in the extraocular muscles of this group were the most marked, the cellular infiltration and the appearance of giant fibers being most accentuated (figures 6 and 7). The nerve endings and motor end plates appeared to be normal. The retrobulbar fat and tissues and the lacrimal glands of occasional guinea pigs appeared to be edematous, but, as in the earlier groups, this finding was not consistent and could not be correlated with the measured exophthalmos.

The study of the glands in this experiment proved of interest. Grossly the thyroids, testicles and adrenals of the injected animals were considerably enlarged over those of the controls. The difference was more than could be explained on the basis of the general slight increase in size of the injected guinea pigs. The average difference in weight was only 14 per cent, but the adrenal glands of the injected group were, on the average, over 50 per cent larger than those of the control animals, while the thyroids and testicles of the injected animals were 40 per cent and 17 per cent, respectively, larger than those of the controls. These findings were borne out in the microscopic studies.

The thyroids of the injected animals possessed large acini, which were filled with dense colloid, and, along with the abundant stroma, gave the appearance of a mild myxedema in comparison with the controls.

The adrenal cortex was thickened and the enlarged cells definitely showed evidence of hyperplasia. The fat was increased throughout the cortex, and a diffuse hyperemia was present. These changes indicated a considerable degree of adrenal cortical stimulation. This seems best explained on the basis of the appreciable amount of adrenotropic hormone known to be present in the Junkmann preparation. Biological assay of this preparation by Moon [5] had shown about 1 unit (20 mg.) of adrenotropic hormone in from 100 to 120 mg. of the Junkmann preparation. Thus a dose of 4 mg. of this preparation, as was used daily in this study, contained from 0.7 to 0.8 mg.

FIG. 6. More advanced myopathy in experimental exophthalmos. The guinea pigs were treated over prolonged periods with the Junkmann preparation of the thyrotropic hormone. The marked cellular infiltration, which is largely perivascular, is well illustrated, as is the loss of cross-striation and separation of muscle fibers. H an E (× 250).

of adrenotropic hormone or approximately one twenty-fifth of a unit. Since doses considerably less than 1 unit are known to be effective, it seems entirely possible that daily doses of one twenty-fifth of a unit might eventually produce very appreciable effects, such as the adrenocortical changes observed.

The convoluted tubules of the testes showed hyperplastic changes and the lumens were occluded with debris and secretion. The pituitary bodies were not unusual, and the deltoid muscle, liver and kidneys appeared to be normal in all animals.

IV. Control experiment to test the possible relationship between exophthalmos and hypothyroidism (thyroidectomized controls). Eleven of 15 guinea pigs weighing between 230 and 370 grams were thyroidectomized. Their weights and the measurements of their eyes were observed over a six months' course in a manner similar to that outlined under Methods. They received no injections, the object of this experiment being to rule out hypothyroidism itself as an etiological factor in the production of exophthalmos. Such a relationship was suggested by the fact that the onset of

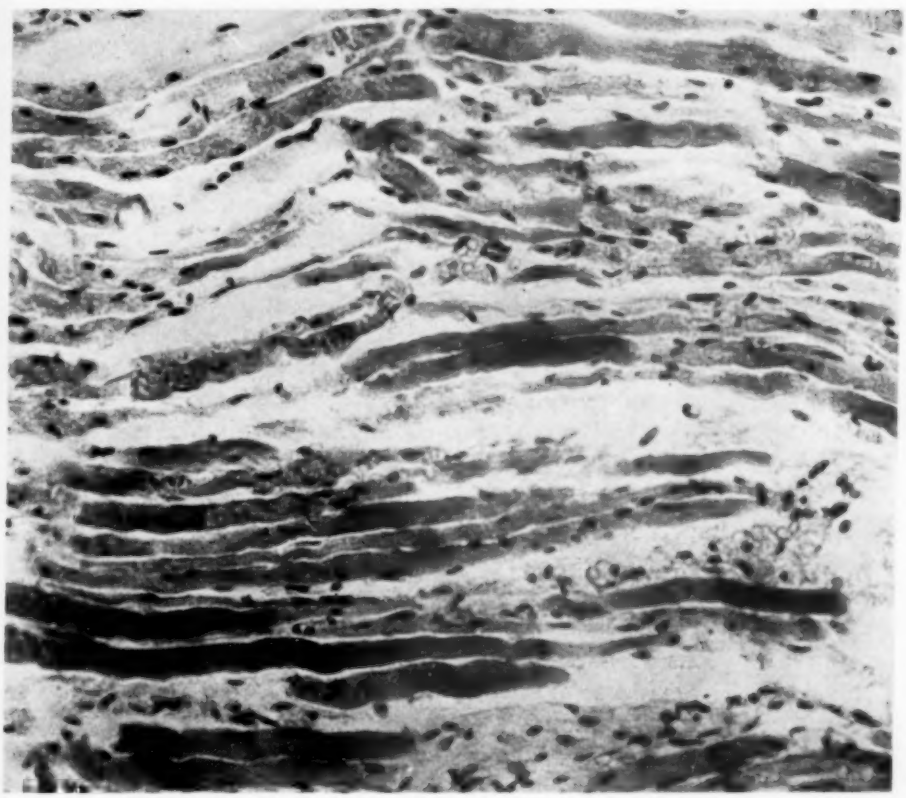

FIG. 7. Myopathy of the extra-ocular muscles of guinea pigs treated with the Junkmann preparation of the thyrotropic hormone, showing the cellular infiltration and unequal staining, loss of cross-striation and separation of the muscle fibers. H and E (× 250).

exophthalmos occurred in two of the previous groups in what was interpreted as a refractory state of hypothyroidism in those guinea pigs surviving the initial period of acute thyrotoxicosis.

Nine of the 11 thyroidectomized guinea pigs survived four months or longer, and of the 18 eyes observed over this period only one suggested any appreciable degree of exophthalmos. This was not borne out, however, in the pathological studies, which showed all the eye muscles to be within the limits of normal. The retrobulbar tissues likewise were found to be normal. Careful search for remaining tags of thyroid tissue was made at the time of the autopsy in all nine thyroidectomized guinea pigs. Single, small, round pieces of thyroid tissue, 0.2 mm. in diameter, were found in three animals. On microscopic examination these bits of tissue showed hyperplastic changes.

The differences in size between the thyroidectomized and control animals at the beginning and end of the experiment, and the differences in size of the organs of both groups were not significant. The adrenals, testes, kidneys, livers and right deltoid muscles appeared normal to microscopic study.

V. Control experiment to test the possible relationship between exophthalmos and the adrenotropic factor of the anterior pituitary body. In the experiments in which exophthalmos was successfully produced, appreciable and effective amounts of adrenotropic hormone were known to be present in the extracts injected. Hypertrophy and hyperplastic changes of the adrenal cortex also occurred. Such changes have been described previously, associated with hyperactivity of this organ. Since adrenocortical hormones are known to play a fundamental rôle in the reactivity of muscle and in metabolism,[6] the possibility of a relationship between these hormones and exophthalmos must be considered. The following experiment was performed to test the possibility of an etiological relationship between exophthalmos and either the direct effect of the adrenotropic hormone on the pituitary body or the indirect effect of adrenocortical hormones elaborated in response to the stimulatory effects of the adrenotropic hormone.

Using the same technic as for the previous groups, eight of 12 male guinea pigs were given daily intraperitoneal injections of 0.5 c.c. of 1 per cent solution of adrenotropic hormone prepared for this study by Moon according to the method described by Lyons.[7] Biological assay showed a potency of one adrenotropic unit per 20 mg. of the powdered preparation, so that the daily dose was estimated to be one-fourth of one unit. Ten other similar preparations of adrenotropic hormone, made and tested by Moon,[5] had failed to show evidence of any thyrotropic hormone. A dose of 100 mg. showed no evidence of stimulation of the thyroid in the squab, although 0.1 mg. of thyrotropic hormone (that is, one part in a thousand of the total dose given) produced a recognizable stimulatory response of the thyroid in this experimental animal. Thus, in the doses used in this experiment, any thyrotropic effect other than that which might be caused by the thyrotropic hormone elaborated by the guinea pig's own anterior pituitary body can safely be ruled out. Although an indirect stimulation of the hypophysis might conceivably be caused by sex hormones formed in excess as a result of the stimulatory effect of androgenic substances (elaborated in turn by the hyperactivity of the adrenal cortex as produced in this experiment), no evidence of the excessive production of thyrotropic hormone, as judged by a study of the thyroid glands, was actually observed in this experiment. Whereas in the previous (thyrotropic) experiment there was a great excess of the thyrotropic hormone in the presence of a slight excess of adrenotropic hormone, in this experiment the reverse was true. Consequently, the failure of the production of any definite exophthalmos in this experiment, as opposed to the exophthalmos observed in the thyrotropic experiment, clearly indicates that the thyrotropic hormone alone was responsible for the production of the exophthalmos.

As might be expected under these circumstances, microscopic study showed the retrobulbar tissues to be normal and the extraocular muscles also were interpreted as being within normal limits. Likewise, the nerve endings and end-organs of the eye muscles showed no changes, nor did other

striated muscles, as judged by the histological appearance of the right deltoid muscle.

It is of interest to note that a retardation of somatic growth, known to result from large doses of adrenotropic hormone,[8] was observed in this experiment, as was gross hypertrophy of the adrenal gland. Although initially the average weight of the injected guinea pigs was 29 grams more than that of the control group, a reverse relationship had occurred toward the end of the experiment, the average weight of the injected pigs being 136 grams less than that of the control animals. Correspondingly, the thyroids, testicles and kidneys of the control group were larger than those of the injected group. The adrenals, however, were grossly 50 per cent larger in the animals which had received the adrenotropic injections. Microscopic study of these glands, stained as previously described with Sudan IV and counterstained with methylene blue, showed the characteristic changes caused by stimulation, namely, hypertrophy and hyperplasia of the cortical cells, an increase in the fat content throughout the adrenal cortex, including the normally fat-free zone intermediate between the glomerulosa and fasciculata, and diffuse hyperemia. The convoluted tubules of the testicles showed slight hyperplastic changes with occlusion of the lumina, in most instances, with cellular debris and secretion.

As already mentioned, no definite evidence of stimulation of the thyroid was observed, the acini appearing within the limits of normal and without evidence of hyperplastic changes. The livers and kidneys were normal. The pituitary bodies are being specially stained and studied by Koneff of the Department of Anatomy of the University of California, and the results are not yet available.

Discussion

The interrelationship of the ductless glands renders an investigation which involves the use of the extracts of these glands a most complex problem. As a result of studies on exophthalmos in rabbits, Marine [9] suggested that thyroid insufficiency and gonadal and androgenic activity, as well as activity of the anterior pituitary, are factors of importance in the production of exophthalmos. It is conceivable that some such pattern of glandular dysfunction is attained when any member of the chain of glands is altered in sufficient degree and manner, and that such changes may result directly or indirectly in the production of exophthalmos. The fact that the thyrotropic hormone may stimulate the thyroid to exhaustion, as was suggested in the studies in which the Squibb preparation and thyrotropic hormone, respectively, were used, would appear to be compatible with this conception. Hypertrophy and hyperplasia of the adrenal cortex were likewise observed in these studies, as was hypertrophy of the gonads in the study utilizing the thyrotropic hormone. The adrenocortical changes, however, may be adequately explained on the basis of the adrenotropic hormone known to be present in appreciable amounts in the extracts used in these experiments.

The gonadal hypertrophy likewise seems best explained on the basis of androgenic hormones resulting from the stimulatory effects of the adrenotropic hormone on the adrenal cortex, as already explained. The control study, in which a potent adrenotropic preparation free from thyrotropic hormone was used, affords strong evidence in support of these points and further suggests that exophthalmos will not necessarily result from changes effected through certain members of the closely related ductless glands. Likewise, hypothyroidism, although known to produce hypertrophy of the anterior lobe of the pituitary body, does not appear to be adequate in itself to produce exophthalmos. This possibility would seem to be ruled out by the control experiment, in which it was found that simple thyroidectomy did not result in exophthalmos. Exophthalmos following thyroidectomy has been reported,[10] but its occasional incidence in slight degree is no more than has been observed in numerous other conditions, both experimentally and in human beings. Alone it does not appear to explain the frequency and intensity of the exophthalmos produced in these experiments.

An etiological relationship between exophthalmos and the gonadotropic factor of the anterior pituitary body seems to have been ruled out by the fact that the gonadotropic factor was not present in significant amounts in the thyrotropic preparation. The testicular hypertrophy in this experiment was caused by the androgenic substance elaborated in the adrenal cortex which was stimulated in turn by the adrenotropic hormone known to be present in the thyrotropic preparation. The successful production of exophthalmos in the experiment in which the Squibb extract was used and in which no testicular hypertrophy was noted, tends to substantiate this conclusion. On the other hand, this by no means rules out the activity of the interstitial cells of the gonads as a possible and necessary link in the production of exophthalmos, as suggested by the studies of Marine.[11]

The growth hormone would appear to be ruled out as an etiological factor in the production of exophthalmos by the fact that proptosis was produced in the original experiment (in which the Parke, Davis preparation was used), in spite of the fact that there was no appreciable increase of weight or size of the injected guinea pigs over their controls. In fact, the guinea pig exhibiting the most marked and consistent exophthalmos in this experiment was notably the smallest and the slowest in development. Also, in the experiment in which the Squibb preparation was used, the increase in weight of the injected animals over their controls was relatively slight (only 5 per cent), and is probably explained on the basis of a mild myxedema. The mammotropic hormone, likewise, can be ruled out, inasmuch as it was not present in significant amounts in the thyrotropic (Junkmann) preparation.

The etiological rôle of the thyrotropic factor in the production of exophthalmos is supported not only by this negative evidence, but by the fact that the most marked exophthalmos was produced by the thyrotropic preparation, in which the dose of thyrotropic hormone was in considerable excess of that given in preparations of whole gland, while other hormones were either eliminated or markedly reduced in relative dosage.

Although the chain of physiological events essential to the production of exophthalmos is not shown by these studies, certain possibilities appear to be ruled out and support is lent to others.

Smelser [3a] and Paulson [3b, 3c] reported changes in the lacrimal glands in their experiments on exophthalmos and, in fact, tended to explain the exophthalmos in part on this basis. Paulson, however, did not report the same changes as Smelser, and those he found occurred to a less extent in his more prolonged experiments. Although changes in the lacrimal glands suggestive of those described by Paulson were occasionally observed in the present studies, the lacrimal glands of the injected group were, in general, both grossly and microscopically indistinguishable from those of the controls. These facts suggest that Paulson observed changes which tended to retrogress after approximately the first three weeks of injection and which returned essentially to normal in the present studies of much longer duration. This course of events is similar to and concurrent with the changes occurring in the thyroid gland, as found by Friedgood [12] and corroborated in the present studies. The persistence and actual progression (in an irregular manner) of exophthalmos over long periods indicates that it probably cannot be explained by changes in the lacrimal glands. Likewise, changes in other retrobulbar tissues were not found to explain the development of exophthalmos. The slight edema occasionally observed in the lacrimal glands and retrobulbar tissues showed no correlation with the measured exophthalmos. The muscle changes recently reported by Paulson [3c] in more prolonged studies are suggestive of the changes observed in this study. His report of maximal proptosis in non-thyroidectomized guinea pigs prior to 10 days of treatment and his explanation of the exophthalmos in terms of retrobulbar edema are at variance with our observations. The shorter duration of his experiments may explain this difference.

In a comparative study of experimental and clinical exophthalmos, Smelser [13] examined the extraocular muscle of six patients with exophthalmos. Although the clinical data for these patients are not presented, enlarged extraocular muscles were found in only two of them, and it is not clear that even these could be classified properly as examples of malignant exophthalmos. His experimental studies, in which guinea pigs were injected with the whole extracts of the anterior lobe of the pituitary body, showed edematous changes of the retrobulbar tissues, especially of the orbital fat, the dorsal lacrimal glands and, to a less extent, the extraocular muscles. Histologically, the extraocular muscles were considered to be normal. The discrepancy between these observations and the present studies, again, would seem to be best explained on the basis of the shorter duration of his experiments.

The evidence thus suggests that the early changes are chiefly edematous in character,[3, 13] while, with continued treatment over prolonged periods, degenerative and pseudo-hypertrophic changes occur. The early edematous changes correspond to the findings described in cases of Graves' disease,[14] while the late degenerative changes, as observed in the present studies, cor-

respond more nearly to a pre-fibrotic stage of the myopathy found in cases of malignant exophthalmos.[1]

The changes found in the eye muscles appear from these studies to be of primary importance. These changes, although relatively slight in comparison with the advanced changes observed late in human patients, seem to be consistent with the lesser degree of exophthalmos obtained in these experiments. Furthermore, the changes in the muscles of the experimental animals appear essentially similar to those found in human beings. It is also of interest that the production and maintenance of exophthalmos over long periods of time result in permanent changes which, contrary to earlier reports based upon short-term experiments, persist during narcosis and after death. The evidence is thus very suggestive that the changes experimentally produced in the extraocular muscles of guinea pigs, by means of the thyrotropic hormone of the anterior lobe of the pituitary body, are essentially the same as those observed in the extraocular muscles of human patients suffering from malignant exophthalmos.

A trial of deep roentgen-ray therapy over the pituitary body in early cases of malignant exophthalmos would be of interest. Indeed, such treatment has already been suggested and favorable results have been reported by Thomas and Woods, Ruedemann and Ginsburg.[15] Only in this way can critical evidence be obtained as to the common etiological relationship between the exophthalmos experimentally produced by administration of the thyrotropic hormone of the anterior pituitary body and the malignant exophthalmos of human beings. Such treatment should be limited to bona fide cases of malignant exophthalmos in which the condition is progressing. It is also suggested by the results of these studies that treatment should be instituted relatively early in the course of the disease. Satisfactory therapeutic results cannot be expected in late cases in which the changes in the eye muscles have progressed to an advanced and irreversible stage.

Summary and Conclusions

1. The exophthalmos experimentally produced by injections of the extracts of the anterior pituitary body was caused by the thyrotropic fraction. Ocular proptosis developed in the refractory period following an acute thyrotoxicosis produced by the action of the thyrotropic hormone on the thyroid gland and progressed slowly in an irregular manner. After several months of injection, the exophthalmos was found to persist in spite of the discontinuance of injections, narcosis or death.

2. Myopathy of the extraocular muscles was observed in the injected guinea pigs which developed exophthalmos. This change was sufficient to account for the degree of exophthalmos observed, as well as its permanence following prolonged treatment. Other satisfactory explanations for the exophthalmos were not found. Qualitatively, the experimental myopathy was consistent with the changes found in the extraocular muscles of human patients afflicted with malignant exophthalmos.

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THE RESPONSIBILITY OF THE AMERICAN COLLEGE OF PHYSICIANS FOR POSTGRADUATE TRAINING*

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THE activities of the American College of Physicians are in accord with the principle that a progressive medical policy on a national scale requires a program of continuous education for the doctors of the nation.

As stated in the Constitution, "The object of the American College of Physicians shall be to establish an organization composed of qualified internists of high standing who shall meet from time to time for purposes of considering and discussing medical and scientific topics, and who through their organization shall attempt to accomplish the further purposes of: (*a*) maintaining and advancing the highest possible standards in medical education, medical practice and clinical research; (*b*) perpetuating the history and best traditions of medicine and medical ethics, and (*c*) maintaining both the dignity and efficiency of Internal Medicine in its relationship to public welfare." So reads Article III, Section 1 of the Constitution.

By way of fulfilling its destiny, the College holds an annual session of one week each year, publishes an outstanding journal, annually awards certain fellowships and honors and for the last four years has offered its membership a series of postgraduate courses.

In the creation of the American Board of Internal Medicine, the College has obligated itself to produce wider opportunities whereby properly qualified aspirants may secure the intensive training and experience which is a prerequisite to certification and fellowship. There is a distinct need for many residencies and fellowships in medicine to furnish adequate facilities for the training of potential internists. Alternative methods of postgraduate training need to be created for men who are not assigned to such appointments.

In the 1938 Annual Report of the Commonwealth Fund, the following significant statement is made: "Whatever the content, the Division believes that postgraduate study is rewarding, if it brings the student into close personal contact with an outstanding and modern-minded teacher; discipleship plays a large part in medical education, if it helps him to make the best use of books and journals and if it gives him a sound approach to diagnosis."

There is no dearth of courses in the general field of postgraduate education. Various State and County Medical Societies throughout the land are conducting excellent courses for general practitioners. The American College of Surgeons and similar organizations are cognizant of their responsibilities to their membership and to those aspiring for membership. The

* Read at the Boston meeting of the American College of Physicians, April 21, 1941.

American College of Physicians has a definite obligation in the field of Internal Medicine.

In a study entitled "Graduate Medical Education in the United States" published by the Council on Medical Education and Hospitals of the American Medical Association, dealing with the years 1937 to 1940, it was found that there were 110 opportunities for practicing physicians to engage in continuation studies in 43 states, in addition to the District of Columbia, during the 1938–39 period. Forty-four of these courses were sponsored by medical schools, including two graduate schools, and seventeen were offered by medical and clinical societies and academies of medicine. While the subjects of general medicine, obstetrics, pediatrics and surgery were featured, opportunities were also offered for continuing study in seven of the more specialized branches of medicine. Ordinarily membership in a County and State Medical Society is a prerequisite for admission. That these courses are filling a definite need is evidenced by the enthusiasm of those enrolled. From 550 to 600 students, on an average, enrolled for all courses of continuation study in each state, according to the A. M. A. survey.

2. The American College and Postgraduate Courses

Where does the American College of Physicians fit into this picture? In 1938—four, two week postgraduate courses were conducted under the auspices of the College with an attendance of 117 men; five courses were given with an attendance of 117 men in 1939; five courses were given with an attendance of 130 men in 1940 and eight courses were given with an attendance of 228 students in 1941.

Organizers of these courses and their colleagues have been united in their appreciation of the high quality of training and experience that students enrolled in these courses demonstrated, and, reciprocally, the students displayed unanimous appreciation for the interest shown by their teachers in the conduct of the courses. The development of facilities whereby outstanding teachers have been brought into intimate association with qualified physicians in search of advanced instruction has been spontaneously successful.

There is no need, nor is it desirable, that the American College of Physicians should carry on a crusade or organize a campaign for the purpose of attracting large numbers of students under pressure of high-powered advertising and publicity. Our College should, however, study the interests and organized activities of other national bodies such as the American Medical Association, the American College of Surgeons and similar groups in order to conserve effort and avoid duplication.

It is reasonably safe to assume that the only national organization chiefly interested in the field of Internal Medicine is our own American College. The rapid increase in the number of men who have signified, by a recent questionnaire, that they are looking to the College for the development of opportunities in this field, suggests that our organization has a responsibility it cannot well evade.

3. The Results of the 1940 Questionnaire

Soon after President James E. Bruce appointed the present Advisory Committee on Postgraduate Courses, a questionnaire, designed to determine the extent of interest of the membership in this field, was sent to every member of the College. Of the 918 questionnaires returned, 593 members signified their desire to attend one or more courses under the auspices of the American College of Physicians; 282 men were definite about taking courses, the balance expressed their desire to attend, if possible. Interest in the various special fields was as follows:

Table I

Cardiovascular diseases and electrocardiography	332
Gastroenterology	136
Allergy	67
Endocrine disorders	61
Diseases of the chest	51
Hematology	47
Metabolic diseases	41
Neurology	33
Arthritis and rheumatism	25
Pediatrics	20
Pathology	10

The following outline demonstrates the growth in interest shown by the College membership, since the inception of these courses in 1938:

Table II

Courses	Time	Conducted By	Attendance		
			Fellows	Associates	Non-Members
1938.					
General Medicine	2 weeks	Harvard Medical School	31	21	3
General Medicine	2 weeks	N. Y. Postgraduate	14	11	
Cardiovascular Diseases	2 weeks	University of Pennsylvania	16	8	
Gastrointestinal Diseases	2 weeks	University of Pennsylvania	7	6	
		Total	68	46	3
				117*	
1939.					
General Medicine	2 weeks	Johns Hopkins and Univ. of Maryland	17	29	5
Cardiovascular and Respiratory Diseases	2 weeks	Johns Hopkins and Univ. of Maryland	11	4	
Cardio-Renal-Vascular Medicine	2 weeks	Northwestern University	7	14	2
Cardiovascular Diseases	1 week	Washington University		11	2
Diseases of the Glands of Internal Secretion	1 week	Washington University	5	9	1
		Total	40	67	10
				117†	

TABLE II—*Continued*

Courses	Time	Conducted By	Attendance		
			Fellows	Associates	Non-Members
1940.					
General Medicine	2 weeks	University of Michigan and University Hospital	18	15	
Medicine In Industry	1 week	Henry Ford Hospital	3	2	33
Allergy	2 weeks	Roosevelt Hospital	2	6	
Hematology	1 week	Ohio State University	22	15	1
Cardiovascular Disease	1 week	University Hospital, State University of Iowa	16	11	
		Total	61	49	34
				144‡	
1941.					
Allergy	2 weeks	Roosevelt Hospital	5	1	2
Gastrointestinal Diseases	2 weeks	Mayo Foundation	18	13	4
General Medicine	3 weeks	Harvard Medical School	21	24	9
Allergy	1 week	Massachusetts General Hosp.	6		
Gastro-enterology	1 week	Evans Memorial, Massachusetts Memorial Hospital, Boston University	22	28	
General Medicine	2 weeks	University of Michigan, University Hospital	10	8	6
Clinical Medicine	1 week	Ohio State University	10	11	5
Cardiovascular Disease	2 weeks	University of Pennsylvania, Graduate School of Medicine and University School of Medicine.	13	12	
		Total	105	97	26
				228§	

In 1938 and 1939 three courses originally offered by the College were withdrawn because of inadequate registrations. In 1941 two courses were withdrawn.

* From forty States, Puerto Rico and Canada.

† From thirty-four States, Hawaii and Canada.

‡ From thirty-three States and Canada.

§ From forty-one States, Panama, Puerto Rico, Canada and Mexico.

From a brief, albeit enlightening, experience in conducting twenty-two courses during the last four years, certain observations have been made:

(1) It is obviously a distinct pleasure for teachers to have such enthusiastic and well prepared students;

(2) The smaller the group, the closer the intimacy between instructor and student;

(3) The students are unified in preferring practical clinical and laboratory experience to didactic lectures;

(4) The students have but a minor enthusiasm for younger teachers whose chief experience has been in theory;

(5) The students deeply appreciate suggestions for collateral reading by their instructors;

(6) The students appreciate the opportunity for social hours at luncheon or in the evening to discuss with their teachers, in an informal way, the various problems and cases of the day;

(7) The two weeks course is the most popular, although a number of men have requested courses of three and even four weeks' duration;

(8) While the majority of student physicians desire the courses just preceding the annual clinical session, a number are interested in taking these courses at other times of the year, particularly the men from the South who request that courses be given late in the Spring or in the early Autumn;

(9) The membership of the College desires to have the courses announced earlier in the year so that appropriate selections and arrangements for participation can be made. There is widespread urge for greater coördination between the courses from year to year and some interest in taking more than one course per year;

(10) Although some of the students attending courses do not go to the annual session, the majority of those in attendance at the courses do not regard the training as a substitute for attendance at the annual session;

(11) A number of officials of the College, men who have had experience in medical education, believe that these courses should be organized on a regional or a community basis.

(12) Too great a formalization of courses is not desirable.

Because of the limited membership of the College, a course may not draw as large a group of students the second year, as the first year it was scheduled. Experience has shown that for the first year a course may be oversubscribed; the second year those who were not able to enroll previously take the course together with a few more, but the demand is somewhat smaller. Students obviously do not wish to repeat the same course year after year. A reasonable solution to this problem would be to repeat courses every second year; for alternate years, courses along similar lines may be organized at different institutions for students who desire yearly instruction in a particular specialty.

4. The Admittance of Non-Members to Courses

Frequently requests have been received from non-members for admission to courses conducted under the auspices of the American College. The Board of Regents has made a rule that only Fellows and Associates of the College be admitted to these courses. However, if there is room up to capacity after all members desiring to attend have enrolled, under certain conditions non-members have been admitted. In view of the fact that these courses are excellen. supplementary preparation for serious minded younger

doctors who are anticipating the examinations to be given by the American Board of Internal Medicine, it may be possible to develop means whereby non-members with proper qualifications and necessary direction, may, upon recommendation by an Officer, Regent or Governor of the College, be admitted to courses.

5. Regencies

Several members of the American College of Physicians whose experience in medical education qualifies them as experts, have suggested the advisability of dividing the United States and Canada into geographical areas known as Regencies. A Regent of the College would be assigned the responsibility of organizing the Governors in his particular Regency into a Regional Committee. In addition to other duties, which are purely of a regional or local nature, the direction of interest of these committees would be to study the needs of the College membership in their section and encourage participation in the problem of postgraduate training. With the continued growth of the American College and the increasing complexity of its executive direction, the Regents and Governors may anticipate heavier responsibilities in the formulation of policies and the conduct of its activities. Even now postgraduate training under the auspices of our organization might be more satisfactorily studied on a sectional or regional basis.

6. Clinical versus Research Training

Officials of the American College of Physicians are uniform in their desire to foster clinical training and develop first class clinicians rather than to concentrate on the training of research-minded laboratory workers. One official stated that it would be easier and more practical to assist in the education of 20 competent internists per year than develop one investigator. Another official believes that postgraduate training by the American College should include the granting of clinical Fellowships whereby younger men would have an opportunity to pursue advanced work along a well coördinated program.

7. Collateral Reading

In certain of the courses, the Directors have given student physicians definite suggestions concerning collateral reading to be carried out in association with their studies. These suggestions have been enthusiastically received. One recalls that collateral reading is an important part in the training of candidates for Fellowship in the Royal Colleges of England, Scotland and Canada.

In view of the endless variety in the quality and quantity of reading material in the broad field of Internal Medicine today, the membership of the College at large would, no doubt, find it generously beneficial if throughout the entire year a course of selected collateral reading might be offered through the Annals of Internal Medicine. This, in effect, would constitute

a reasonably satisfactory extension course for many of the members who cannot avail themselves of opportunities for participation in postgraduate training. A number of university departments throughout the nation are today conducting similar courses in collateral reading to the eminent satisfaction of a large following.

8. Final Impressions

Probably the major objective of the American College of Physicians lies in the field of medical education. This, as explained by President Bruce, should consist of postgraduate opportunities whereby its members may be kept constantly abreast of medical progress, and, also, longer and more intensively arranged opportunities by which suitable aspirants may prepare themselves for specialism in Internal Medicine and its allied fields.

Valuable as postgraduate courses are in the maintenance of standards already achieved, they are but supplemental to effective graduate courses of study, whether the latter be formal courses now existing, or an orderly arrangement for study with competent men in well organized hospitals with university or medical school affiliations.

The American College of Physicians is the only organization whose principal interest is the continuous training of the internist.

The American College of Physicians is primarily interested in training clinicians rather than research students or teachers.

The Committee on Postgraduate Courses has recommended that for the next year the following courses be offered under the auspices of the College:

(*a*) General Medicine	—2 courses—	2 weeks in duration.
(*b*) Allergy	—2 courses—	2 weeks in duration.
(*c*) Cardiovascular Disorders	—2 courses—	2 weeks in duration.
(*d*) Gastroenterology	—2 courses—	1–1 week; 1–2 weeks in duration.
(*e*) Arthritis and Rheumatism	—1 course —	1 week in duration.
(*f*) Tuberculosis	—1 course —	1 week in duration.

In view of the growth of the College and the increasing complexity of the problem of postgraduate studies, it is recommended that a regional division of the College be considered.

The possible curtailment of courses depends on the national situation. Courses in collateral reading should be developed and published in the Annals.

The American College should consider ways and means, as suggested in a resolution by the Board of Regents at their December 1940 meeting, for offering courses in advanced medicine for the personnel of army hospitals associated with the mobilization of the nation's resources.

In establishing the habit of scholarship, under capable guidance, the student physician in the final analysis must be his own teacher.

CASE REPORTS

RUPTURE OF AORTA INTO THE PULMONARY ARTERY WITH LONG SURVIVAL *

By Paul D. White, M.D., F.A.C.P., Francis L. Chamberlain, M.D., and Saul R. Kelson, M.D., *Boston, Massachusetts*

Case Report

Joseph Meranda, negro, 74 years old at death in 1938, a Cape Cod cranberry picker, entered the Massachusetts General Hospital in November 1933, in his seventieth year, because of ulcers of the right leg following varicose veins and an infected scratch of a year before. He had had no dyspnea, chest pain, or palpitation, but examination revealed moderate enlargement of the heart, aortic systolic and diastolic murmurs, a blood pressure of 195 mm. mercury systolic and 55 mm. diastolic, a positive Hinton reaction, and by roentgen-ray slight aneurysmal dilatation of the ascending aorta (figure 1 A). In three weeks he was discharged with the ulcers almost wholly healed after treatment by rest, potassium iodide and mercury by mouth, and soothing ointments to the leg. He continued the potassium iodide and mercury for a few months.

Early in January 1937, a little over three years later, he was taken ill with what he thought was a cold, accompanied by palpitation and dyspnea to the point of orthopnea. A short rest in bed helped temporarily, but a few months later, in April, he grew much worse, with substernal pain and restlessness quickly followed by edema of the legs. In May 1937 he reëntered the Massachusetts General Hospital very ill. His heart was found to be much larger; the murmurs were described as before; and the roentgen-ray (figure 1 B) showed marked prominence of the pulmonary artery and lung hilus shadows not present in the earlier picture. He improved rapidly under rest, digitalization, and salyrgan diuresis, and was discharged in a few days. He remained improved for six months.

In January 1938, he rapidly grew worse again and reëntered the hospital in February in severe congestive failure. Physical examination is said to have shown the same auscultatory findings as before, but this time an "aortic" systolic thrill was noted in addition. The blood pressure varied from 130 to 180 mm. mercury systolic and measured about 60 mm. mercury diastolic. The electrocardiogram was not remarkable. On February 2, Dr. Sprague noted that the murmur and thrill in the pulmonary area were really continuous and not just systolic and diastolic as previously described. On February 8, we hazarded the diagnosis of "rupture of an aortic aneurysm into the pulmonary artery." This, we went on to say, "and only this, will explain the continuous character of the murmur and thrill in the pulmonary valve area and the appearance by roentgen-ray of a marked bulge in the pulmonary conus not in the least apparent in 1933. Careful fluoroscopy when he improves enough to allow it would help in establishing or rejecting this diagnosis. The murmur sounds like that of a patent ductus arteriosus which, condition, however, was not evident by roentgen-ray in 1933." Fluoroscopy on March 1 confirmed this impression.

* Received for publication May 1, 1941.

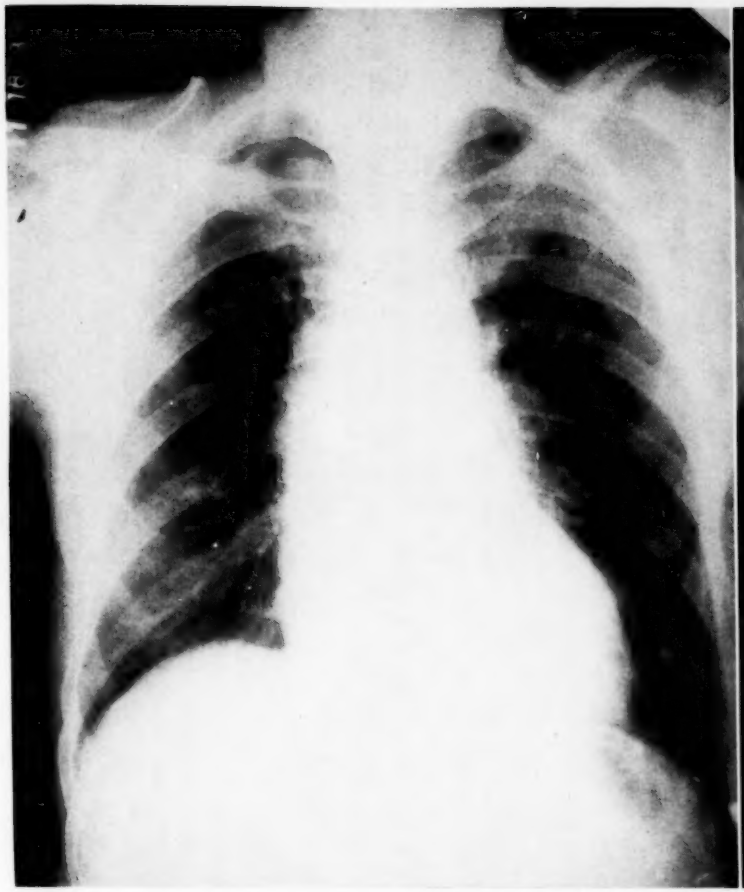

FIG. 1 A. Roentgen-ray film showing slight cardiac enlargement and slight widening of the great vessels of J. M., November 1933.

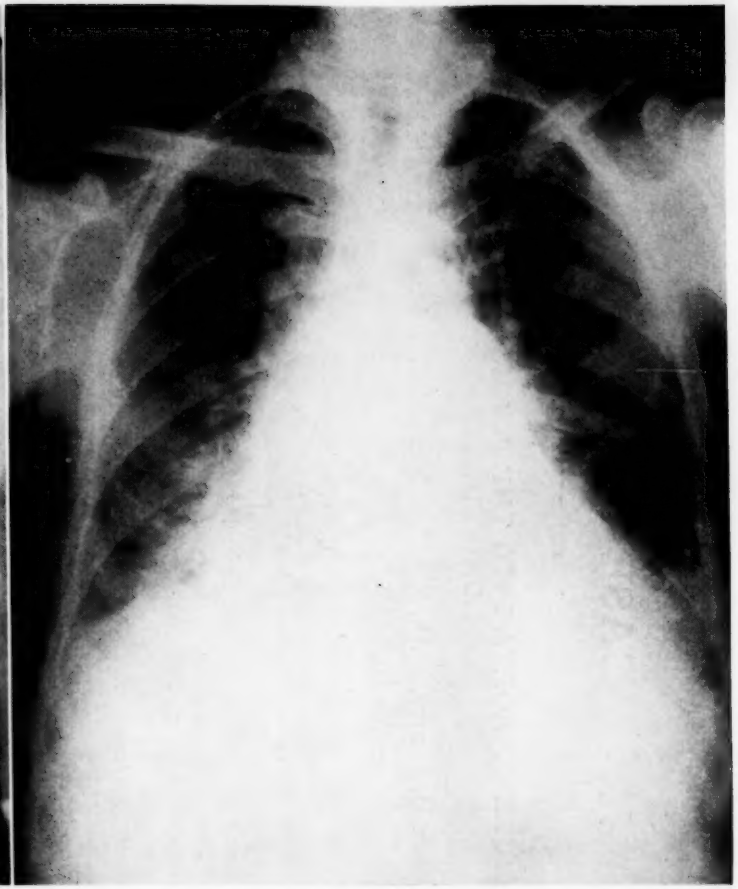

FIG. 1 B. Roentgen-ray film showing marked increase in heart size particularly with bulging in the region of the pulmonary artery of J. M., May 1937.

FIG. 2. Anterior view of right ventricle and right auricle of J. M., opened to show normal valves, hypertrophied and dilated ventricle, and a small hole just above the pulmonary valve connecting the pulmonary artery with the aorta. Probe is shown inserted into this opening.

He continued completely crippled with heart failure after he went home and died on October 7, 1938, 21 months after the onset of his heart symptoms and eight months after the clinical diagnosis was made of rupture of an aortic aneurysm into the pulmonary artery.

AUTOPSY

The body was that of a well nourished, 74 year old male negro, slightly over six feet tall and weighing approximately 200 pounds. The heart weighed 885 grams, and was greatly enlarged in all diameters, with particular prominence in the region

FIG. 1 A. Roentgen-ray film showing slight cardiac enlargement and slight widening of the great vessels of J. M., November 1933.

FIG. 1 B. Roentgen-ray film showing marked increase in heart size particularly with bulging in the region of the pulmonary artery of J. M., May 1937.

of the pulmonary conus. Its cavities had approximately three times normal volume, and all valve rings were dilated. The left ventricular wall measured up to 19 mm. in thickness, the right up to 7 mm. The mitral and tricuspid valve cusps were slightly edematous but otherwise negative. The pulmonary valve appeared normal. The aortic valve was slightly thickened along its free edge. The aortic sinuses were greatly dilated, with a few small nodular calcific deposits at the base of the right and posterior cusps. The myocardium showed no gross scarring on section.

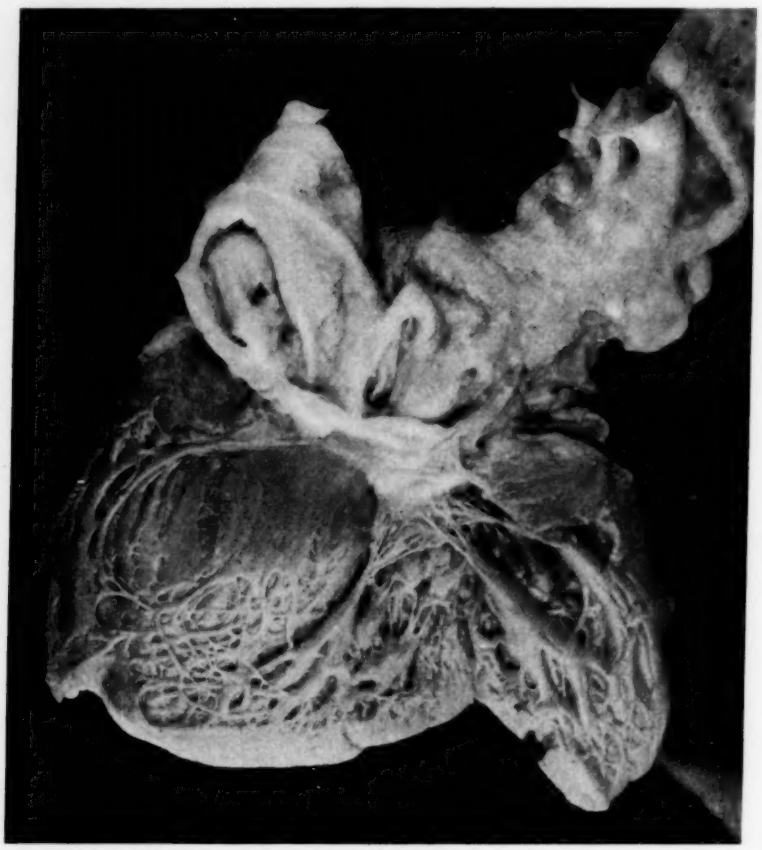

FIG. 3. View of left ventricle and aorta of I. M. opened to show much dilated left ventricle, normal mitral valve, essentially normal aortic valve and dilated aorta with an aneurysmal pouch at the left in which is seen an opening leading into the pulmonary artery.

Coronary Arteries. The orifice of the right coronary artery was completely occluded by syphilitic and atherosclerotic scarring, and the vessel itself was small and collapsed. The left coronary artery ostium was highly placed, 1.5 cm. above the aortic ring; this artery was patent throughout and showed only very slight atherosclerosis.

Pulmonary Artery. The pulmonary artery was markedly dilated, measuring 8.5 cm. in circumference at a level 3 cm. above the pulmonary valve ring. Five mm. above the insertion of the valve cusps and slightly posterior and to the right of the right anterior pulmonary valve commissure was a roughly oval opening 5 mm. by 6 mm. with smooth, slightly raised margins (figure 2). The artery was otherwise free.

FIG. 4. Closer view of aneurysmal pouch of aorta with sinus leading into the pulmonary artery.

Aorta. There was marked diffuse aneurysmal dilatation of the ascending aorta and arch, and to a lesser extent, of the descending portion. The aorta and arch showed changes typical of syphilitic aortitis: there were numerous linear, puckering, spoke-like crenations, and smooth pearly elevated patches, with many soft yellow atheromatous deposits, ulcerated in places. Above the right posterior commissure was a secondary saccular aneurysmal pocket 2.3 cm. across by 2.8 cm. high by 2.1 cm. deep, with thickened smooth edges. A probe within the right coronary artery passed behind and above this sac to an occluded orifice immediately to the right. Above the commissure between the right and left anterior cusps was a less sharply defined secondary aneurysmal pouch, measuring 3.5 cm. across, by 4.0 cm. long, by 2.0 cm. deep, with a small out-pocketing from its upper right margin. In its anterior lower margin, 1.5 cm. above the aortic valve ring, was a smooth-edged oval opening, surrounded by puckered yellowish plaques. This opened into the pulmonary artery (figures 3 and 4), and was the same opening previously described there. Above and slightly to the left of the posterior aortic cusp, with its lower margin 1.7 cm. above the free edge of the cusp, was a smooth-lipped opening into the aortic wall, 9 by 7 mm. This ended in a blind pocket in the septum between the aorta and right auricle, with a depth of 3 mm., partly filled with projecting irregular clot. The descending aorta measured 7.5 cm. in circumference, and showed numerous atherosclerotic plaques but very few puckerings suggesting syphilis. Atheromatous changes were most plentiful in the abdominal aorta, particularly at its bifurcation, where ulceration was extensive.

Venae Cavae. The venae cavae appeared normal.

Microscopic Examination. Myocardium: The heart muscle showed one small area of fibrosis. The small branches of the coronary arteries appeared normal.

Aorta: The aortic wall showed perivascular lymphocytic infiltration characteristic of syphilis. There was fragmentation of the elastic fibers with medial degeneration and hyalinization. There were areas of intimal thickening and hyalinization, and extensive areas of cholesterol deposit deep in the media, with necrosis of the surrounding tissue and a few small foci of calcification in the media.

Discussion

In the last 25 years there have been a dozen case reports of this rare condition, the last one in 1938. Before 1913 there had been about 50 cases on record. Only two previously, so far as we know, have been definitely diagnosed antemortem; a porter aged 35 by Wade of England in 1861, and a negro aged 29 years reported by Scott of Cleveland in 1924.* However, the chief diagnostic clue, namely, the development of a continuous murmur in the pulmonary valve area, was clearly pointed out by James Hope in 1839 in the third edition of his work on diseases of the heart and great vessels.

Our case was relatively easy to diagnose because of the long survival and the opportunity we had to examine the patient before and after the rupture (including the comparison of the roentgen-ray films). The long survival was doubtless due in part at least to the small opening from the aorta into the pulmonary artery.

Of the 13 cases noted in the last 25 years, six were negroes; only five of the 13 lived more than two months after the beginning of symptoms. The duration of life in the 13 cases was apparently three for a few hours, one for 24 hours, one for three weeks, another for three weeks, and the others for five weeks,

* Since this report was written another case has been correctly diagnosed antemortem by Dr. William Porter of Richmond, Va. (personal communication).

two months, four months, four months, nine and a half months, 11 months, and 4 years respectively; the last case was not correctly diagnosed antemortem. Thus our case was very unusual with his survival of 21 months after the onset of symptoms and eight months after the correct clinical diagnosis. The case that survived a long time (4 years) had a smaller opening, 7 mm. in diameter.

Summary

A case is reported of a negro who died of heart failure at 74 years of age, 21 months after the onset of cardiac symptoms and eight months after the correct clinical diagnosis was made of rupture of a syphilitic aneurysm of the ascending aorta into the pulmonary artery. This case is of note first and especially because of the unusual longevity both in age of patient and in survival after the rupture, and second, because only two cases previously had been correctly diagnosed antemortem. The clinical diagnosis of a small rupture of the aorta into the pulmonary artery was apparent from the combination of the development of a continuous murmur in the pulmonary valve area, the bulging pulmonary artery by roentgen-ray, and the rapid appearance of congestive heart failure without early fatality in a negro with known syphilitic aortitis.

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A FATAL CASE OF BESNIER-BOECK-SCHAUMANN'S DISEASE WITH AUTOPSY FINDINGS *

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New facts are forever widening the horizon of knowledge. What is thought to be pathognomonic of a disease today may be changed tomorrow to a presumptive sign or, with new data, may present an entirely new syndrome or disease complex.

These statements are strikingly applicable to a hodge-podge of syndromes which have been unfolding themselves during the last half century and have been reported by Besnier,[1] Boeck,[2] Schaumann[3] and others. A disparity of views has resulted because only a small part of the complete knowledge was known at any time. It is comparable to Aesop's fable concerning the color of the chameleon. Erythema induratum of Bazin (1861), the chillblain lupus of Hutchinson (1888), the lupus pernio of Besnier (1889), miliary lupoids and sarcoids of Boeck (1899), subcutaneous sarcoids of Darier-Roussy (1904), granuloma annulare of Little (1908), angio-lupoid of Brocq and Pautrier (1913), and several other types of skin lesions were at first considered as variations of lupus. Although there is still a wide divergence of opinion as to the nature of some of the above mentioned skin conditions, they have been gradually separated from the definitely tuberculous lesions such as the tuberculides, the miliary lupoids of Boeck, and others. Schaumann further set apart the chillblain lupus of Hutchinson, the subcutaneous sarcoids of Darier and Darier-Roussy, granuloma annulare and skin conditions attributable to syphilis, and retained only the lupus pernio of Besnier and the large nodular sarcoids of Boeck as a part of a new disease entity which he has called "benign lymphogranulomatosis" in contrast to the malignant form of Hodgkin's disease. Pautrier[4] at first included most of the above mentioned forms in the true sarcoids but, as shown by Tillgren,[5] he has gradually come over toward Schaumann's point of view. In 1934 he still retained "the subcutaneous sarcoids" in addition to lupus pernio and Boeck's large nodular sarcoid.

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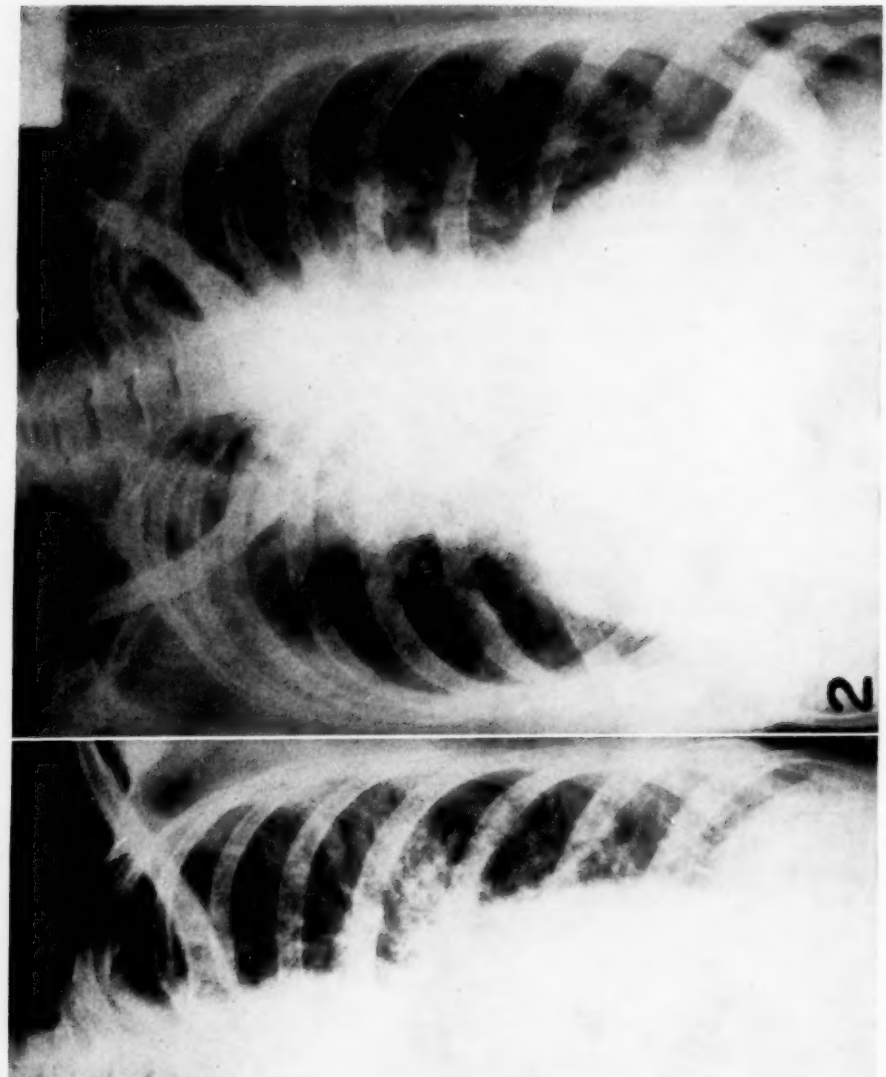

FIG. 1. (1) Roentgenogram taken April 13, 1937, revealing an appearance of "fibroid" tuberculosis. (2) Another roentgenogram, taken January 9, 1939. There is a great deal of clearing of parenchymal lesions but a pronounced increase in the density out from the midline on the right side.

Without doubt the greatest advance with regard to the nature of "sarcoids" was the pronouncements of Schaumann that they were part of a systemic process. At first Boeck suggested that they might be systemic, but later retracted the suggestion. The bone lesions were the first observed apart from the skin lesions, but were not at first understood as part of a systemic disease. Although Kienbock (1902),[6] Kreibich (1904),[7] Bloch (1907),[8] Rieder (1910),[9] and Jüngling (1921) [10] reported bone lesions alone or associated with lupus pernio, Schaumann (1914) [11] was the first to consider them as part of a general process wherein there is usually a lymphadenopathy, as well as lung and tonsillar lesions. Less commonly there may be skin lesions, bone and marrow changes, enlarged spleen and liver, lesions of the mucous surfaces, the uveal tract, the parotid, and many other organs of the body. There is nearly always a mononucleosis associated with the other lesions. It seems to be logical that the adenopathy should appear as part of the first generalization of the disease, with lung, skin, bone, and other lesions appearing at various intervals later.

The greatest controversy has taken place regarding the nature and cause of "sarcoids." Many French clinicians (Darier,[12] Pautrier,[13] Gougerot,[14] et al.) have considered that the disease is a reaction of the host and not caused by any single agent. Among the probable causes they mention tuberculosis, leprosy, syphilis, foreign bodies (paraffin, vaseline) and leishmaniasis. Some feel that it is caused by a filtrable form of the tubercle bacillus while others consider, with justification, that the cause is still unknown.

Kissmeyer [15] believes that sarcoid is due to an unknown virus with effects ranging between those of leprosy and tuberculosis. Kuznitzky and Bittorf [16] think it is a disease sui generis. Schaumann at first felt that it was such a condition, but later considered it due to tuberculosis possibly of the bovine type. The trend now seems to be in favor of a tuberculous origin, though there are many other widely different theories. It does seem, that in view of the variations of the tubercle parasite, which have been demonstrated by many bacteriologists, there may well be variable pathologic and clinical effects depending upon these variations.

Many cases have now been followed for years in which there has been a gradual change noted from the "sarcoid state" or "benign lymphogranulomatosis" of Schaumann to some form of tuberculosis with a demonstration of the parasites, a changing of a negative to a positive tuberculin reaction, and along with this and perhaps as a result of it, the occurrence of caseation. Kyrle [17] among others has followed the aging of the lesions from the early focal point of lymphocytes through the appearance of monocytes to the development of giant cells. The latter forms mature and disintegrate, after which fibrosis develops in the old focus. Kyrle also reports the presence of tubercle bacilli during the early stages of development but a disappearance of the bacilli as the nodules reach the stage of giant cells and fibrosis. Our own work at the Municipal Tuberculosis Sanitarium has partly borne this out as well as permitted us to observe other additional phenomena of even greater interest.

Most observers are agreed with respect to the histology of sarcoids. In fact, there is little other choice because the findings are quite constant. The lesions consist of miliary nodules that form first as monocytic accumulations and then develop into Langhans' giant cells with a few lymphocytes. The giant cells become older, get large and disintegrate, leaving a fibrous nodule without caseation.

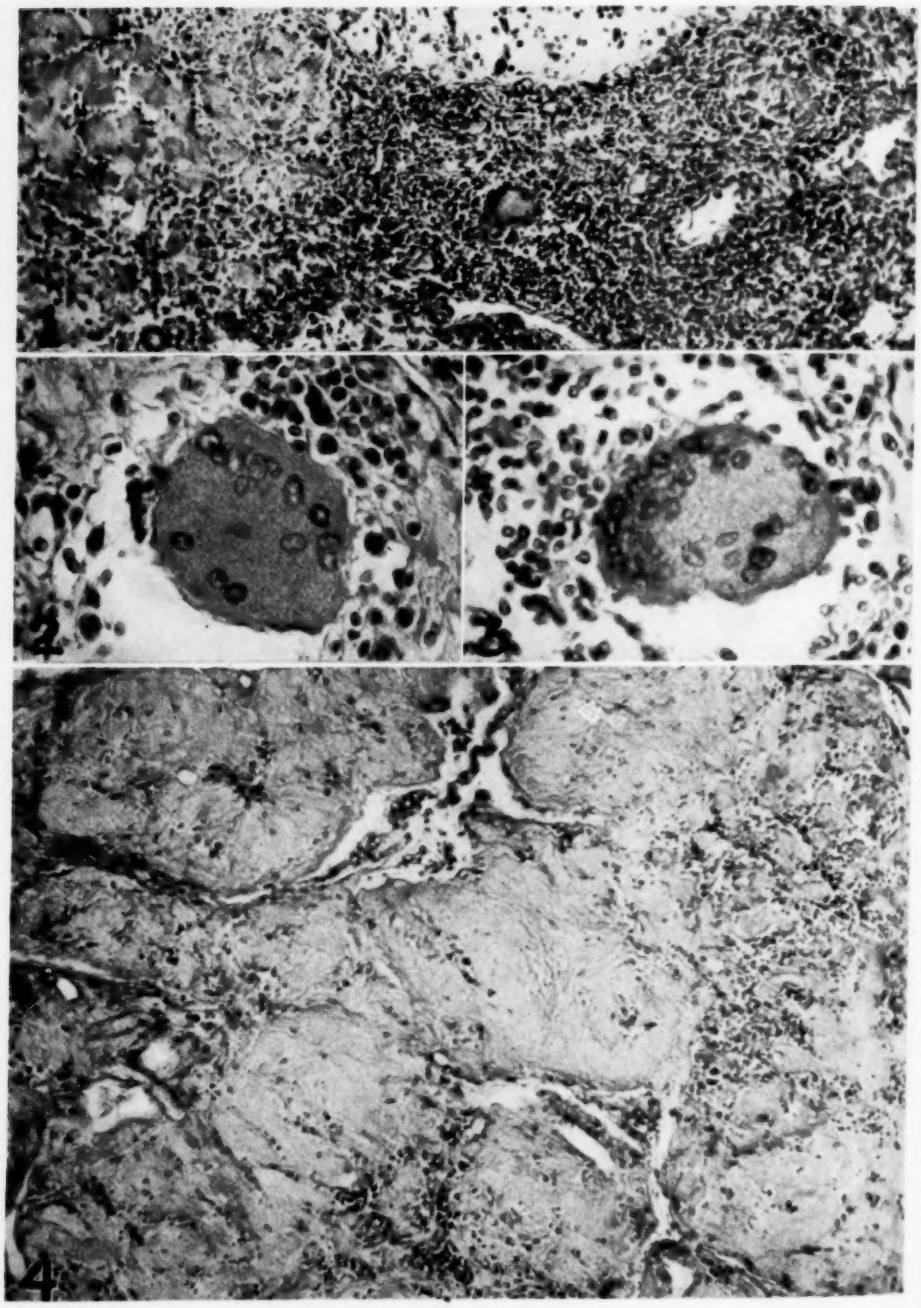

FIG. 2. (1) A photomicrograph of section of lymph node showing small foci of inflammation, hyaline connective tissue fibers, and Langhans' giant cell. × 130. (2 and 3) Two "old" giant cells undergoing disintegration. × 400. (4) Fibrous residue in a lymph node in which the lesions have run their course. × 120.

Because of these characteristics, Mylius and Schürmann [18] have used the cumbersome term of "widespread sclerosing tuberculous giant cell hyperplasia." Much more appropriate is Pinner's [19] term "non-caseating tuberculosis."

The presence of caseation is ordinarily understood to rule out the diagnosis of sarcoid. However, as certain cases become tuberculous, they develop caseation; when they do, they automatically cease to be "non-caseating." Likewise, in the opinion of many, they would cease to be "sarcoid." It is obvious that the terminology cannot be definitely settled until the etiology and complete course of the disease are known.

The important feature in this report concerns the lung lesions, especially those of a late evolutionary stage. Although Schaumann first mentioned lung lesions in 1914, Kuznitzky and Bittorf, in 1915,[16] deserve most credit for an accurate description of the process.

The early lung lesions appear on roentgenograms usually as soft nodules simulating disseminated tubercles or small soft infiltrates with an associated hilum lymph node enlargement. These lesions are perhaps the same as the vast number of benign miliary tubercles of the lung, or healed miliary tuberculosis described as *miliare froide* by Sayé and Burnand, as *miliaris discreta* by Neumann, and in still other terms by others. As the lesions become chronic there is a disappearance of their "soft" nature and the appearance of a stringy and net-like fibrosis over the entire lung fields, especially out from the hilum. A late emphysema usually appears. The microscopic appearance corresponds to these findings. There is a transition from the cellular nodule to the fibrotic one.

The report we are about to make concerns strictly the roentgen-ray and pathological findings of the lungs, although there are other useful data concerning the gross findings in the other organs, and the clinical course. Due to the fact that much of the clinical data was not available, no claim at completeness is made for anything except the roentgen-ray and the pathological findings in the lungs and thoracic lymph nodes.

There is a secondary interest in the heart lesions also because of the effect which the lung fibrosis exerted on cardiac function. Nothing was observed in the way of specific heart lesions, as reported by Salveson.[20]

Owing to the fact that few autopsies have been reported on this condition, no efforts should be spared to report every case about which any complete data are available. Only 18 autopsies had been reported by 1938, according to Pinner.[19] Spencer and Warren [21] have added one since. Although there is much of interest in the gross findings in the organs, microscopic notes are available only for the lungs and lymph nodes. While no skin lesions were ever reported and no observations, clinical or pathological, were ever made which indicated the presence of other lesions than those in the lungs and hilum lymph nodes, it must be admitted that a more complete history and a more complete microscopic study might have revealed facts that were not evident.

Case Reports

The patient, a 45 year old woman, was seen by one of us (T) in consultation with Dr. John W. Tope on April 16, 1937. She had been ill four months with cough and dyspnea, but no fever. Six sputum examinations were negative for tubercle bacilli. Two recent roentgen-ray films revealed mediastinal shadows, more on the right than on the left. There were irregular infiltrations in the lung fields. There

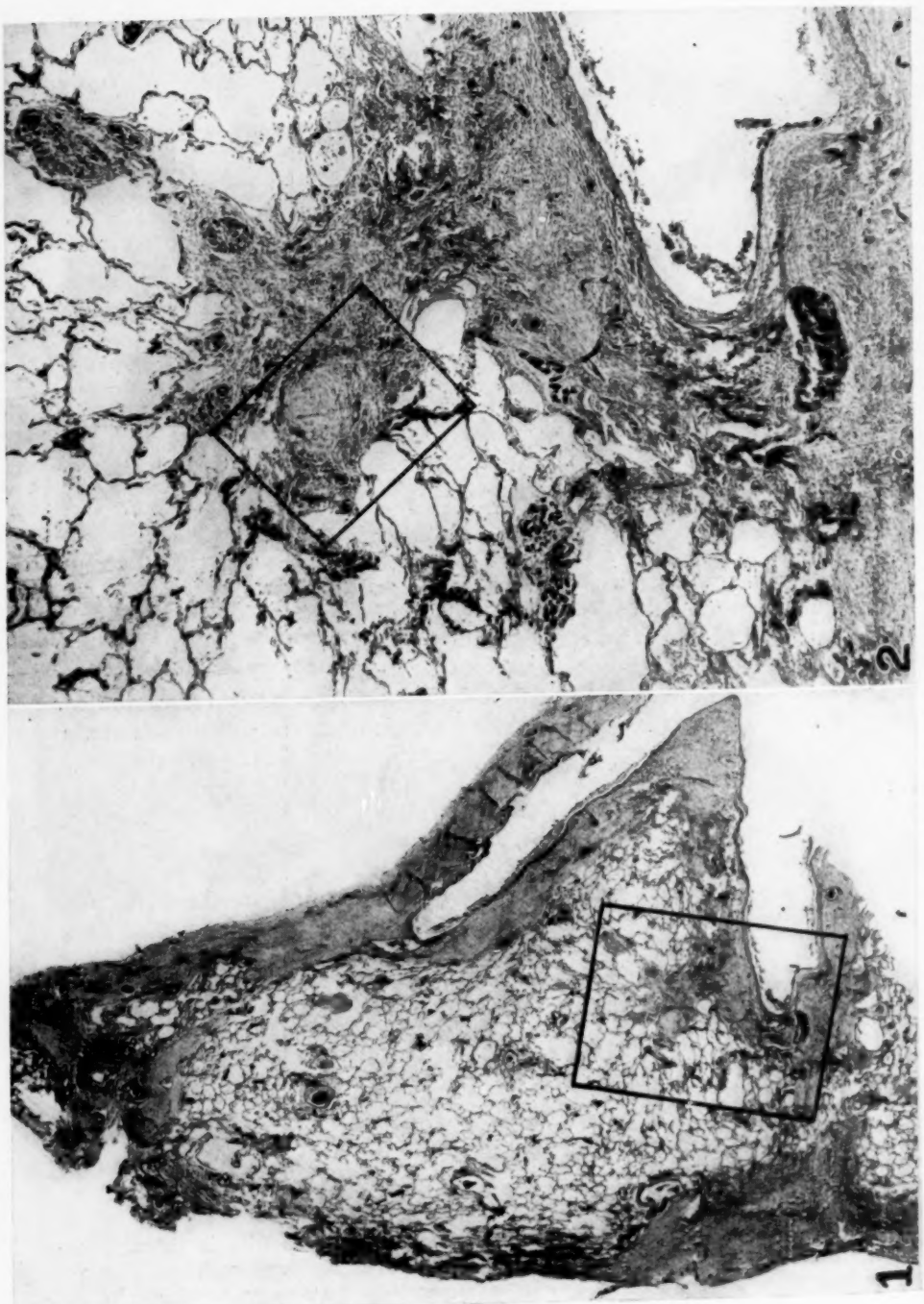

FIG. 3. (1) A low power photomicrograph of lung tissue. Note the marked perivascular fibrosis. ×8. (2) An enlargement of the part outlined in part 1. The focal nature of the fibrosis is more evident. Early lesions may be seen in the lymphoid tissue in the right hilus zone. ×3

were no cervical or axillary glands and no enlargement of the spleen. The earlier diagnosis by Drs. Tope and French had been pulmonary tuberculosis. Because of the negative sputums and rather characteristic hilum shadows a diagnosis of Hodgkin's disease was made, for which the patient subsequently received roentgen-ray therapy which temporarily relieved her dyspnea. At a later date her dyspnea apparently recurred and a reported diagnosis of Ayerza's disease was made.* She was sent to Valmora Sanatorium where death occurred suddenly in bed on March 6, 1939.

The first roentgenogram was taken April 13, 1937. The bony framework appeared normal except that there was a droop to the right shoulder and a slight narrowing of the intercostal spaces on the right side. There was a slight scoliosis. The heart was partly concealed in a hazy jagged mass around the hilum. The right hilum was much more involved than the left. There was a partly consolidated mass extending from the apex to the base paralleling the spine and extending laterally several centimeters. The upper and middle lobes were extensively involved in a large nodular and infiltrative involvement that appeared almost confluent except in the apex. The nodules were on the average about 5 mm. in diameter, but were irregular, had hazy and irregular borders, and seemed to blend out into the perivascular shadows. The lower lobe was also involved in a similar manner but only to about one-half the density. No definite annular shadows were visible. In the left lung there were dense streamers of densities extending from the hilum out toward the axilla and to a lesser extent toward the apex and base, flanked by the same vague irregular nodules described on the other side.

A roentgenogram taken September 20, 1937 revealed a slight clearing of the nodular densities with a slight exaggeration of the perivascular shadows.

A roentgenogram taken September 8, 1938 revealed an extension of the atelectasis at the right base half way across the visible lung field, and then up toward the hilum where a large mass was observed protruding outward. There was a fading off of the density toward the apex. Outside of a few nebulous clouds in the right upper lobe and an increase in the left hilum density, there was little change.

The last roentgenogram, taken January 9, 1938, showed an exaggeration of the condition described before. The hilum mass at this time extended half way out and the basal mass three-fourths of the way out to the lateral wall. The scoliosis was exaggerated; the trachea was pulled over to the right. The upper lobe was more dense, but a few irregular clear spaces appeared in the midfield which were perhaps emphysematous bullae rather than true cavities. The left side was not greatly changed.

An autopsy was performed by Dr. R. Yale Lyman, and the protocol was furnished through the courtesy of Dr. C. H. Gellenthien of Valmora, New Mexico.

Autopsy. G. W. was a white female housewife who was 48 years old at the time of death. The diagnoses on admission to the sanatorium were pulmonary tuberculosis, Hodgkin's disease, Ayerza's disease and mediastinal tumor.

The external examination revealed a slender emaciated white female about 50 years of age. There was a slight yellowish pigmentation of the skin. The hair was brown and the pupils dilated.

There was moderate kyphosis of the thoracic spine. The abdomen was flat. The remainder of the external examination was negative.

Examination of the thoracic cavity revealed 200 c.c. of straw-colored fluid in the left pleural cavity and 500 c.c. of reddish fluid in the right. There were adhesions between the anterior surface of the pericardium and sternum.

The right lung was contracted and drawn to the right side of the mediastinum. The left lung overlapped the mediastinum to the right border of the sternum. There was a fatty globular remnant of the thymus located in the superior ventral portion of the mediastinum.

Fig. 3. (1) A low power photomicrograph of lung tissue. Note the marked perivascular fibrosis. × 8. (2) An enlargement of the part outlined in part 1. The focal nature of the fibrosis is more evident. Early lesions may be seen in the lymphoid tissue in the right upper corner. × 30.

* Since the preliminary report it has been learned that Dr. E. E. Irons was responsible for this accurate clinical observation.

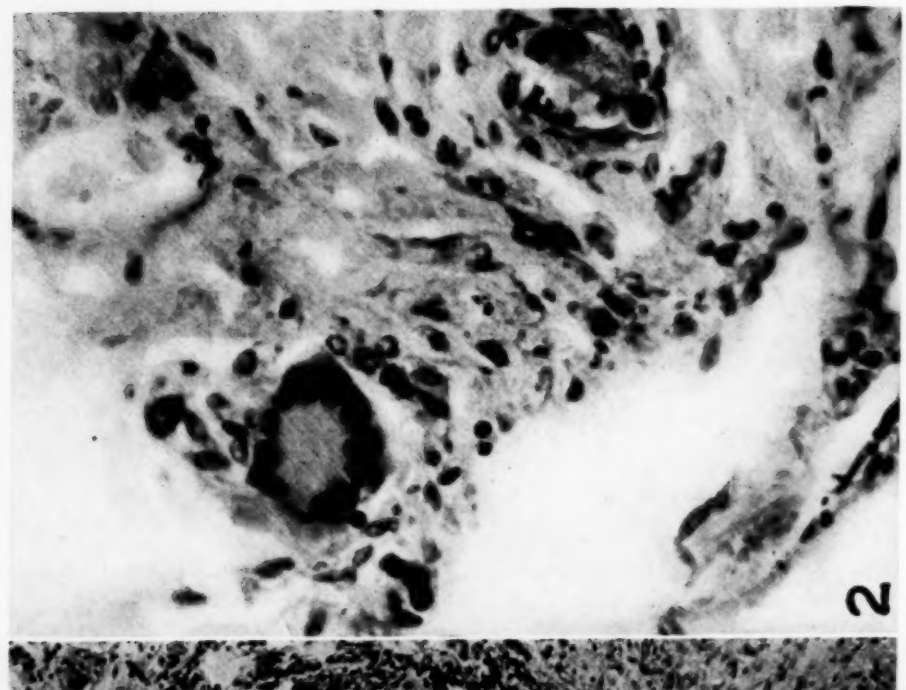

FIG. 4. (1) A higher power of the area outlined in figure 3 (2). Note the whorl of fibrous tissue and the perifocal chronic inflammation with Langhans' giant cells. × 130. (2) An enlargement of the area on the left upper part of part 1, showing a typical Langhans' giant cell. × 400.

The pericardium contained 200 to 300 c.c. of straw-colored fluid. There were several atheromatous plaques in the transverse portion of the aorta.

The heart was 4 cm. to the right border of the sternum and weighed 450 gm. It measured 18 by 15 cm. The right auricle was dilated and filled with blood. The wall of the right ventricle was 4 mm. in thickness, and the wall of the left 20 mm. The valves were normal except that there was a slight thickening and slight calcification of the aortic and mitral valves. The left ventricular wall was markedly hypertrophied. The interventricular septum was thickened. The musculature was red-brown.

The left lung weighed 675 gm. The pleura was shiny, moist and mottled with grayish areas. There was no evidence of adhesions. There were several black calcified hilum lymph nodes and a grayish mucopurulent secretion in the bronchi.

The right lung weighed 620 gm. The superior lobe was markedly contracted. There was a nodular, firm middle lobe, contracted and fibrotic. Along the mediastinal borders of the right lower lobe were several blebs. There was crepitation of the lower lobe. The upper lobes were firm and noncrepitant. There was a cavity 2 by 1 by 1 cm., surrounded by a markedly fibrotic capsule.

The spleen weighed 115 gm. and appeared normal. The left kidney weighed 115 gm., was markedly sclerotic, and the capsule was adherent to the cortex which was gray-brown and 8 mm. in depth. The right kidney weighed 145 gm., was pale red and firm with an adherent capsule. The cortex was 6 mm. in depth. The liver weighed 1650 gm., was pale mottled reddish-brown. It had sharp borders, and on section was a pale purplish-gray.

All other organs and tissues were essentially normal.

The organs were sent to Dr. Kirschbaum of the Cook County Hospital, Chicago, for diagnosis, and he kindly sent sections and lung tissue to us for study.

Lymph Nodes. Section 1. There were small foci of fibrous tissue throughout, about two-thirds of the section. The foci appeared to have formed in the germinal centers of the lymph nodes. They were made up of several broad bands of fibrous tissue coiled in the focus, and sometimes several of these were grouped together. The number of fibers varied up to a large number in which instances they formed fibrotic nodules. Around them were varying amounts of lymphoid tissue in which were situated a few giant cells in different stages of evolution from early monocytic clusters to large disintegrating forms. The architecture of the node was badly deranged. No pigment was present.

Section 2. There was much less fibrosis, but the architecture was deranged throughout. Beneath the capsule on one side there were patches of fibrosis as observed in the first section. In other parts the capillary walls were partly hyalinized, and there were smaller and earlier foci of fibrous tissue with an occasional early giant cell. The lymphoid cells were greatly diminished in numbers. There was no pigment in this node.

Section 3. There was much black pigment present indicating relationship to the bronchi. There was one small fibrotic nodule 1 mm. in diameter which resembled a tubercle that had become fibrotic but not caseous. It was composed of solid nodules of fibrous tissue filling up nearly all the node, leaving practically no lymphoid or germinal elements. There were a few atypical giant cells present.

Lung Parenchyma. Section 1. The sections were all badly torn but the architecture was fairly normal. The alveoli were not greatly distended and their walls were not overly thickened. Around some of the smaller vessels and beneath the pleura were small fibroid plaques of fibrous tissue that were not densely hyalinized. Outside of some of these smaller plaques was an occasional giant cell. In one or two places throughout the section were much larger areas of fibrosis. The fibrils were not especially arranged in any constant form. The pleura was thickened and there were

mation with Langhans' giant cells. × 130. (2) An enlargement of the area on the left upper part of part 1, showing a typical Langhans' giant cell. × 400.

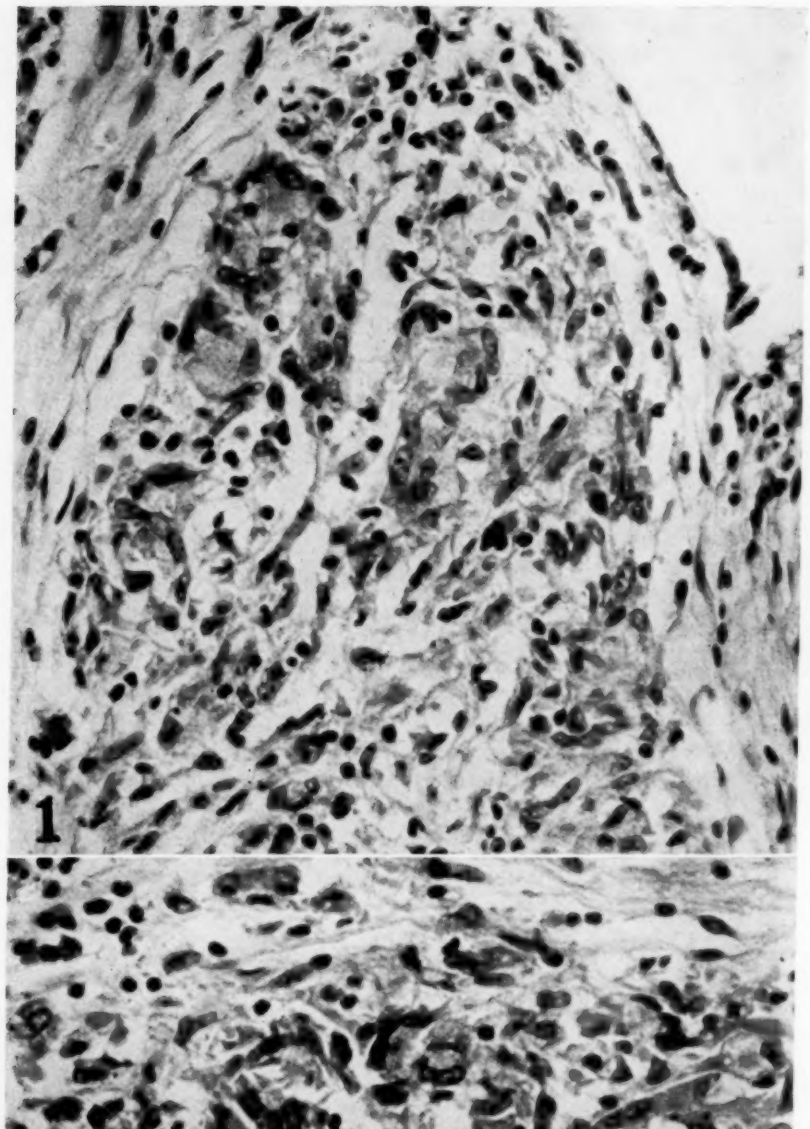

FIG. 5. (1 and 2) Photomicrographs of the early lesion in the lung parenchyma revealing monocytes becoming arranged into atypical giant cells. × 400.

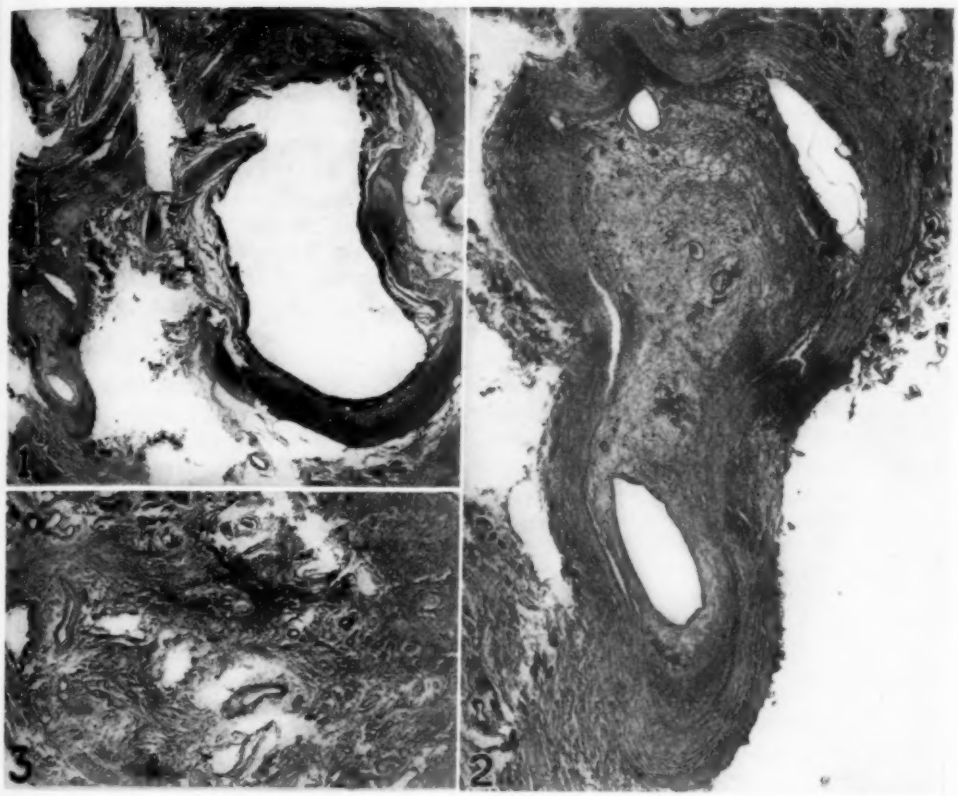

FIG. 6. (1) A low power photomicrograph of the lung hilum across a large bronchus revealing a large pulmonary artery undergoing closure by an endarteritis. × 8.5. (2) An enlargement of the artery shown in part 1. × 35. (3) The atelectatic lung tissue. × 8.5.

plaques of fibrosis occasionally along the pleura, some of which followed down some of the blood vessels. Certain alveoli were filled with serous exudate.

Section 2. Another section of lung tissue was made up of alveoli that had undergone extensive atelectasis. Practically no normal alveoli could be found. Many of the smaller arteries were completely obliterated by endarteritis. Much brown pigment was scattered throughout. Beneath the pleura in one or two places heavy tortuous masses of fibrous tissue dipped into the parenchyma. The vessels not only showed fibrosis within the lumen but a surrounding zone of periarteritis.

Section 3. This was a similar section with almost complete fibrosis. There was an occasional dilated bronchiole. Much black pigment and heavy bands of fibrous tissue were seen in all parts of the sections surrounding practically all of the vascular and bronchial structures. On one side there was a dense nodule of fibrous tissue that had the appearance of an old fibrotic tubercle. There was no caseation, but much pigment was present. The lesions in this section were apparently older than in any other of those examined.

Section 4. This section revealed bronchi some of which were undergoing dilatation while some were completely obliterated by fibrous contraction. The mucosa of these showed only a few disintegrated goblet cells remaining. The lumen was practically gone. There was heavy fibrous tissue present throughout.

Section 5. A section near the margin of the lung revealed a heavy marginal fibrous layer which at various points along the pleura dipped into the lung structure. There were heavy fibrous bands which followed the arteries toward the hilum. Some of the smaller arterial capillaries were surrounded by rings of heavy fibrous tissue. There were zones of cellular infiltrate bordering the perivascular fibrous tissue. In such zones were numerous irregular giant cells, some composed of three or four pinched nuclei in a bed of lymphoid tissue, while others were complete horseshoes or circles. Most of them were irregular and imperfect but nevertheless were definitely the Langhans' type of giant cells. Some of the smaller capillaries were surrounded by small and recently formed foci of lymphoid structures in which were many monocytic cells that were just beginning to suggest the formation of giant cells.

Hilum. Section 1. Cross section of a larger bronchus revealed a marked amount of surrounding fibrous tissue localized especially about the arteries. One of the main arteries contained what appeared to be an old thrombus that had become organized and recanalized by two or three small vessels. It was possible, however, that the occlusion was due to a progressive endarteritis.

Section 2. Another pulmonary section of a bronchus revealed another large artery that had become completely obliterated, only one or two very small capillaries being present in the lumen. The peribronchial and periarterial regions were composed of dense fibrous tissue in which there were numerous capillaries containing blood cells.

Discussion and Conclusions

In spite of a sketchy history the postmortem evidence of the lung and lymph nodes was sufficient to warrant the opinion that the patient suffered from a systemic disease corresponding to the *benign lymphogranulomatosis of Schaumann.* Death was due to destruction of lung tissue by the lesions of sarcoid as well as to an endarteritis of some of the main branches of the pulmonary artery, leading to cardiac failure. The disease in this instance was apparently healed or healing at the time the heart failed.

The pulmonary vascular obstruction probably led to symptoms of Ayerza's disease. While the heart was enlarged to twice its normal size and the aortic and mitral valves were thickened, the changes were probably secondary and not due to the general disease.

No skin lesions were ever reported and no lesions other than those of the lungs and hilum lymph nodes were found. No acid-fast bacilli were ever found and no caseation was present anywhere in the postmortem material.

This case, therefore, bears out Schaumann's contention that the disease may come on silently, without external lesions, and that it is perhaps first and predominantly a lymph node disease, later involving certain other organs and tissues. The facts also reveal that the process may be a fatal disease in spite of the paucity of symptoms and generally benign character of the usual case.

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MICROCOCCUS TETRAGENUS MENINGITIS; REPORT OF A CASE AND REVIEW OF THE LITERATURE*

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THAT *Micrococcus tetragenus* infections are rare is evidenced by the fact that relatively few cases have been reported in the American literature, and that Reimann, reviewing the foreign journals up until 1935, recorded a total of only 170 cases. During the past five years three cases [2, 3, 4] have been reported in American journals and an equally small number from Europe. The infrequency of the infection is further shown by the fact that all the reports are concerned with one to three cases with the exception of two mild separate epidemics [1] affecting 70 soldiers during the World War, 1914–1919. The first reports of *Micrococcus tetragenus* infection in this country were made by Griewe in 1899 and Steele in 1914.

The *Micrococcus tetragenus*, a gram-positive organism occurring in tetrads, first described by Koch and Gaffky in 1881 and often called by the latter's name,

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is found as a normal saprophyte in the mouth, nose and throat, and occasionally in pulmonary tuberculous or abscess cavities. Jakowski [5] in 1886 was the first to report on its pathogenicity and low powers of virulence. The organism has a predilection for serous membranes, producing inflammation and suppuration. With lowered resistance of the patient it tends to invade the lymphatics or blood stream and produces abscesses in remote serous cavities and parenchymatous organs. From a clinico-pathological aspect, the close resemblance to staphylococcic infections is apparent and because of the close bacteriologic resemblance to staphylococcus the diagnosis may often be difficult.

The infection is most common in infancy and among virile young adults. The sex ratio is generally about three males to one female. Sore throat and respiratory infections, anemia, typhoid fever, undulant fever, streptococcic infections, alcoholism and prolonged heat exhaustion have been noted as important predisposing factors lowering the resistance of the patient. The reason for the low incidence among the aged and debilitated cannot be explained. The onset of the disease is usually abrupt and in cases with septicemia, a sharp chill precedes the fever of a remittent type, ranging from normal to 106° F. Although only a few of the reported cases have shown positive blood cultures, it is reasonable to assume that the metastatic abscesses which may occur in any organ, particularly in serous cavities, are due to blood stream invasion. Those areas most frequently reported as sites of localization are: nasal sinuses, lungs, pleura, pericardium and endocardium, middle ear, peritoneum, joints, fallopian tubes, endometrium, kidneys, bladder, colon and least frequently the meninges. The symptoms and physical findings are those of infection with suppurative inflammation at one or several sites of localization. Among Reimann's collected series, patients with fulminating infections have died within seven to ten days and in others the disease has run a course as long as seven months. In cases with septicemia the mortality rate is about 50 per cent. Since there are no characteristic signs of *Micrococcus tetragenus* infection and specific agglutinins in the patient's serum are often of low titer or absent, recovery and growth of the organism from the infected tissue are the only positive method of diagnosis.

This report is concerned with one case of *Micrococcus tetragenus* meningitis with septicemia, which terminated fatally following the added complications of pneumococcic and streptococcic meningitis. This case is of interest not only because of its rarity and unusual clinical course but also because it is one of the first to be evaluated for the effect of the sulfonamide derivative drugs on the course of the infection. In 1939, Criscietello [3] reported the first case of *Micrococcus tetragenus* meningitis treated by sulfanilamide with recovery.

A survey of all the literature reveals 14 previously reported cases of *Micrococcus tetragenus* meningitis; the first by Bezancon and Lepage [6] from Paris in 1898, the remainder by Boettinger [7]; Pende [8]; Vincent [9]; Perfetti [10]; Ramond [11] two cases; Leschke [12]; Griewe [13]; Bonnano [14]; Blum [15]; Reimann [1]; McGowan [2]; and Criscietello.[3] The salient features of these cases are shown in table 1.

Case Report

G. M., aged 50, white, married housewife, following a right sided rhinorrhea of several months' duration was found in June 1939 to have a carcinoma of the right antrum which on biopsy showed epidermoid carcinoma, Grade II. A Caldwell-Luc antrotomy with drainage was done and this was followed during the next four months

TABLE I

Case	Sex	Age	Predisposing Factor	Onset	Duration	Clinical Signs	Blood Culture	Spinal Fluid Culture	Agglutinins	Treatment	End Result	Other Findings
Bezancon and LePage 1898	F	?	Puerperal sepsis	Epileptic attacks	1 Mo.	Hemiplegia, coma and fever					Fatal P.M.-Meningitis Cult. *Micro. tetra.*	
Griewe and Mitchell 1899	M	35		Sudden	3 Wk.	Meningitis		Pos.			Fatal	None
Boettinger and Malloizel 1906	M	58	Pleurisy	Sudden	5 Da.	Meningitis		Pos.		Lumbar puncture	Fatal p.m.	Pleura culture pos. for *Micro. tetra.*
Pende 1908	F	48	None	Sudden	25 Da.	Meningitis		Pos.		Lumbar puncture	Fatal	None
Vincent 1908	F	?	None	Gradual	10 Da.	Cerebral		Pos.		Lumbar puncture	Recovered	None
Ramond and Resibois 1915	?	?	None	Sudden	Sev Da.	Respiratory vaso-motor		Pos.		Lumbar punct.; injection of colloidal gold	Recovered	None
Ramond and Resibois 1915	?	?	None	Sudden	Sev. Da.	Vomiting		Pos.		Lumbar punct.; injection of colloidal gold	Recovered	None

TABLE I (*Continued*)

Case	Sex	Age	Predisposing Factor	Onset	Duration	Clinical Signs	Blood Culture	Spinal Fluid Culture	Agglutinins	Treatment	End Result	Other Findings
Perfetti and Monziols 1918	M	?	Pyodermia	Sudden	6 Wk.	Mixed localization	Pos.	Pos.		Lumbar puncture	Fatal p.m.	Peritonitis, pericarditis, renal abscesses, bone abscesses
Leschke 1919	M	23	Sore throat	Sudden	7 Da.	Meningitis, arthritis	Pos.	Pos.		Lumbar puncture	Fatal	None
Blum 1923	M	15	None	Sudden	3½ Mo.	Meningitis	Pos.	Pos.	1/2000	Lumbar punct.; autogenous vaccine	Recovered	Nephritis, cystitis
Bonnano 1931	M	28	None	Sudden	4 Wk.		Neg.	Pos.			Recovered	None
Reimann 1935	M	46	Sore throat	Sudden	7 Wk.	Meningitis	Pos.	Pos.		Lumbar puncture	Recovered	Joints, prostate
McGowan and Kinsner 1939	M	40	Heat exhaustion	Sudden	5 Wk.		Pos.	Pos.	Pres.	Lumbar punct.; meningococcus serum	Recovered	?
Criscietello 1939	M	18	None	Sudden	3 Wk.			Pos.		Lumbar punct.; sulfanilamide	Recovered	None
Authors'	F	50	Post-oper. sinusitis	Sudden	6 Wk.		Pos.	Pos.		Lumbar punct.; sulfanilamide drugs	Fatal p.m.	None

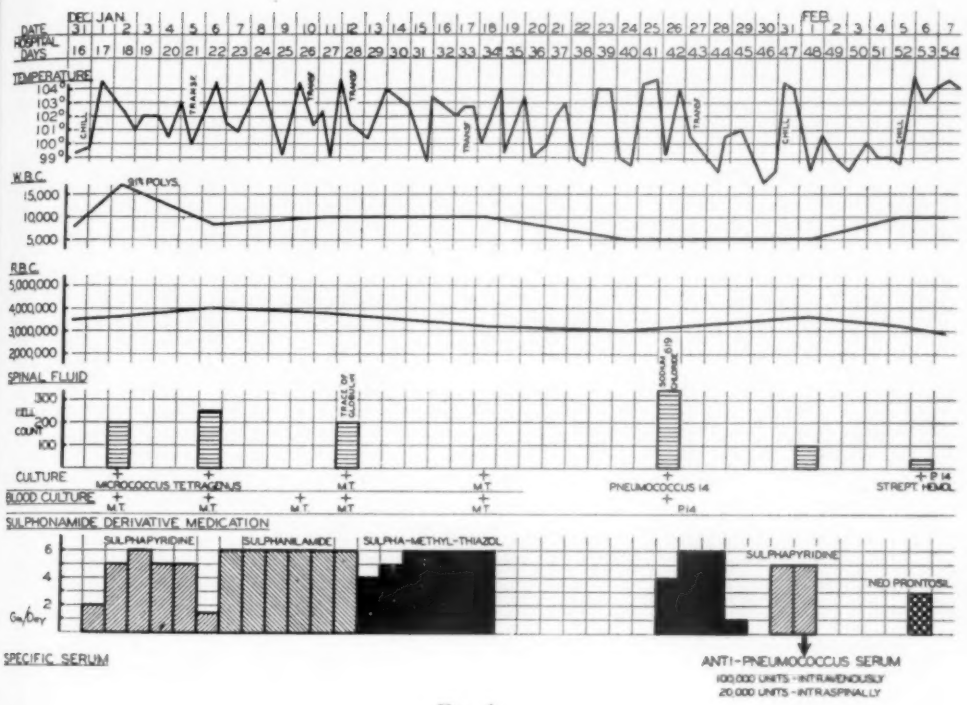

FIG. 1.

by several courses of external and peroral roentgen-ray therapy plus radon seed implantation into the antrum. Because of the extensive involvement of the floor of the orbit by cancer and marked proptosis of the eye, a cautery excision of the roof of the antrum was performed on 12/15/39 followed in one week by exenteration of the orbit. Except for low grade fever with toxicity, the post-operative course was uneventful for two weeks.

On 1/1/40 following a sharp chill the patient developed a fever of 104° F. and became irrational. There was moderate neck rigidity, exaggerated deep tendon reflexes and positive Kernig and Babinski signs. At the lung bases there were inconclusive signs of an early pneumonitis. Following a lumbar puncture showing turbid fluid under normal pressure, a presumptive diagnosis of pneumococcic meningitis was made and a course of sulfapyridine medication, one gram every four hours, was begun.

On 1/2/40 the blood and spinal cultures were reported as showing a pure growth of an atypical coccus which after several days of study proved to be *Micrococcus tetragenus*. The medication was then changed to sulfanilamide but signs of septicemia and meningitis continued unabated and at the end of 12 days blood and spinal fluid cultures were still positive for *Micrococcus tetragenus*. The antral cavity was carefully debrided and irrigated several times daily with Dakin's and sulfanilamide solutions. About the optic foramen and base of the orbital defect there was considerable infection, with necrotic bone fragments and slough. On several occasions, gentle debridement of the slough was followed by an immediate chill and fever which led us to believe that this area was the focus of infection and that by eradication of this focus the source of the meningitis would be removed.

On 1/12/40 the medication was changed to 6 grams of sulfa-methyl thiazole daily but after six days spinal fluid culture was still positive. Although the patient was mentally alert and showed no physical signs of meningitis during the next two weeks

fever persisted and repeated lumbar punctures every three to four days showed slight turbidity. All specimens were positive for *Micrococcus tetragenus.*

On 1/31/40 following a severe chill the signs of meningitis recurred with headache, fever and neck rigidity. Cultures of the blood and of a cloudy spinal fluid showed Pneumococcus type 14. The patient was then given 120,000 units of antipneumococcus type 14 serum intravenously with 20,000 units intraspinally and intravenous injections of 5 grams of sodium sulfapyridine on two successive days. Immediately the temperature returned to normal. There was a clearing of the sensorium, signs of meningitis rapidly subsided and for the first time the blood and spinal fluid cultures were negative.

For three days the course was normal. Then she had a sharp chill followed by a temperature of 105° with recurrent signs of meningitis. Lumbar puncture gave a slightly turbid fluid which on culture showed a predominant growth of hemolytic streptococci and a few colonies of Pneumococcus type 14. Because of severe nausea and vomiting 20 c.c. of 5 per cent neoprontosil was administered intravenously and intramuscularly but the patient failed to respond to medication and supportive treatment and died on 2/7/40.

Postmortem Findings: Gross and microscopic examination of the nasal sinuses and cervical lymph nodes showed no residual carcinoma. On removing the brain, the dura and meninges were markedly inflamed and thickened due to congestion and edema. Two distinct types of meningitis were apparent from the type of the cerebral exudate present. Over the frontal lobes the exudate was a thin glarey brownish fluid. Extending posteriorly from the Sylvian fissures and on the inferior surface of the brain was a thick yellow-green purulent exudate. On opening the right sphenoid sinus 5 c.c. of thick greenish pus under pressure drained into the cranial cavity. Purulent material was easily expressed from about both optic tracts. The roof of the right sphenoid sinus was necrotic and the base of the hypophysis was surrounded by purulent exudate. The apparent route of migration of the infection was from the nasopharynx or orbital cavity to the sphenoid sinus and thence along the optic tracts and through the roof of the sphenoid sinus to the hypophysis and meninges. Section of the brain showed no abscesses. Microscopic examination confirmed the gross findings. Culture of the meninges showed Pneumococcus; unfortunately no cultures were taken from the sphenoid sinus.

The diagnosis of *Micrococcus tetragenus* meningitis is primarily a bacteriologic problem. Since this organism on smear may be confused with staphylococcus or meningococcus, the diagnosis depends entirely on recognition of the organism's cultural peculiarities. From previous case studies it is seen that the clinical characteristics of this type of meningitis are with few variations the same as seen in meningococcic meningitis. Significant in the differential diagnosis is the presence of all cocci in an extracellular position and the rapid growth of the *Micrococcus tetragenus* on culture. However, these are not conclusive.

The peculiar properties of bacterial dissociation or pleomorphism exhibited by this organism are its most characteristic feature as is demonstrated by studies in this case and also by Reimann [1] and McGowan and Kinsner.[2] Initial blood and spinal fluid cultures gave a pure growth of gram-positive cocci occurring predominantly in tetrads, growing in delicate translucent colonies which on standing 48 to 60 hours became opaque white and yellow. Later cultures gave a growth of only scattered white colonies in which the organisms appeared in single diploid and clump formations, showed marked variation in size and stained mainly gram-negative. On first thought, this was believed to be due to bacterial attenuation resulting from the drug therapy, but after reviewing the studies of Reimann [1, 16, 17]

this was accepted as being characteristic of the bacteria. About some of the older colonies on blood agar, a greenish color with slight hemolysis was noted. The organisms characteristically failed to liquefy gelatin and fermented none of the sugars.

The few immunologic studies carried out in cases with this infection demonstrate that the production of antibodies in the human is variable and inconstant. In two cases reported by Kramar [18] and Meltzer [19] agglutinin titers as high as 1–500 and 1–640 were reported. Blum's case of meningitis [15] with septicemia and cystitis showed agglutinin titers varying from 1–300 to 1–2000. However, in cases reported by Von Oppenheim [20] and Reimann [1] no specific agglutinins were found in the patient's blood and intradermal injection of a prepared vaccine failed to produce a reaction. Studies by McGowan and Kinsner [2] showed that the bacterial suspensions in low titer were agglutinated by polyvalent anti-meningococcic serum but showed no reaction with the patient's own serum. In this case bacterial suspensions in standard dilutions mixed with the patient's serum failed to show any agglutination or precipitation both by microscopic and macroscopic technic.

McGowan has found the *Micrococcus tetragenus* to be non-pathogenic for animals, but according to Reimann's immunologic studies in animals [1, 16, 17] each bacterial variant evokes specific agglutinins and precipitins in low titer. Animal studies throw no light on the variable immunologic responses seen in humans. However, a review of cases suggests that antibodies appear in the blood stream if the infection is prolonged for several months.

The value of sulfanilamide drug therapy for *Micrococcus tetragenus* infections is questionable. In Criscietello's case of meningitis [3] treated by sulfanilamide with recovery, the one blood culture taken one week after therapy was begun was negative and therefore inconclusive. In this instance, septicemia persisted in the presence of an undrained purulent sphenoid sinusitis so that one is unable to estimate accurately the bacteriostatic effect of the drug therapy, but it may correspond roughly to the weak bacteriostatic effect of the drug noted by Long and Bliss [21] on in vitro cultures of *Micrococcus tetragenus*. It is interesting to observe that the administration of anti-pneumococcus serum after 33 days produced the first negative blood and spinal fluid cultures along with complete remission from symptoms. Since effective antibody formation has been demonstrated in a few cases of long duration, the autogenous vaccine therapy used in three cases of generalized infection with septicemia with recovery reported in 1920 by Ludke [22] impresses one as rational specific therapy for this disease, particularly in the low grade chronic form. It is doubtful that it would offer help for the acute fulminating type of infection.

The distinctive feature of this case was the development of infection in a postoperative orbital and antral defect with the development of an unsuspected sphenoid sinusitis. The organisms spread either by the blood stream or by lymphatics along optic nerves and through the roof of the sphenoid and infected the meninges. Previous to the development of the streptococcic meningitis it was our clinical impression that this patient was steadily improving and would make a full recovery. The autopsy findings clearly show: (1) the pathogenesis of the successive meningeal infections, (2) the reason for failure to improve after intensive sulfanilamide therapy and (3) the need for careful search and elimination of any focus of infection. The presence of some purulent and necrotic

slough in the base of the orbital defect which when debrided was followed by fever and chill, made us believe that this was the only focus of infection producing the meningitis. If the hidden focus of bacteria in the sphenoid sinus had been discovered and drained early it is reasonable to assume that the terminal pneumococcic and streptococcic meningitis would have been prevented and the patient would have recovered.

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EDITORIAL

EDEMA

THE basic etiologic causes of the production of generalized edema are much better understood than even ten or fifteen years ago and the treatment administered is on an improved physiologic basis. By a differential diagnosis we are able to determine more accurately the cause of the edema and thereby institute a more logical therapeutic program.

When edema is present, a number of possible conditions must be considered and after a careful analysis of the history and the physical and laboratory findings an accurate diagnosis is possible in most cases. Conditions commonly producing edema are glomerulonephritis, both the acute and chronic stages, and nephritis associated with the nephrotic syndrome. Cardiac disease with congestive failure must be considered as an etiologic condition in edema and frequently both cardiac disease and nephritis coexist. Other conditions not so common, but which must be considered as possible causes of the edema, are hepatic cirrhosis, polyserositis, myxedema, malignant growths and lymphedema. Space will not permit a discussion of the differential diagnosis of these various conditions but suffice it to say that when the correct diagnosis is made the treatment is usually definite.

Perhaps the most classical type of edema and the type that usually responds most satisfactorily is that produced by chronic glomerulonephritis with the nephrotic syndrome. In these cases the renal function per se is usually good and the edema is due largely to enormous loss of protein in the urine, a lowered serum protein and a lowered colloidal osmotic pressure resulting in retention of salt and water in the tissues. The treatment is directed toward correcting this situation by restoring the physical and electrolytic balance in the body. The patient is given a high protein, salt-free diet which is low in fluid. This provides for 100 to 125 gm. of protein a day and 800 to 1,000 c.c. of fluid. Potassium nitrate, 6 to 12 gm. daily, is a satisfactory diuretic salt and one that does not disturb appreciably the acid base equilibrium. As a " physiologic splint " to increase temporarily the colloidal osmotic pressure of the blood until serum protein is formed as fast as it is lost in the urine, from 90 to 150 gm. of acacia can be given. As a rule 500 c.c. of 6 per cent solution of acacia in 0.06 per cent solution of sodium chloride are given intravenously on successive or alternate days for three to five injections or until the concentration of acacia in the blood is about 2 per cent. This, in addition to the 3 to 5 per cent concentration of protein in the serum in these cases produces a sufficient colloidal osmotic pressure in most instances to result in adequate diuresis and gradual elimination of fluid and salt from the body. Even when the patient is taking a salt-free diet, as much as 24 gm. of salt have been eliminated in the urine in a day. It is not un-

common to observe an output of from 3 to 5 liters of urine in twenty-four hours. It is seldom necessary to resort to mercurial diuretics with this program.

Of late considerable attention has been directed to the use of dried plasma and to lyophil serum in preference to acacia. Lyophil serum seems more toxic than solution of dried plasma. Rarely does either a solution of dried plasma or one of acacia cause unpleasant reactions. Solution of acacia has the advantage of being more economical, easier to obtain and prepare and remains in the blood stream a longer time. Reactions from acacia seldom occur if a pure solution is used. Blood transfusions present similar problems and in addition necessitate careful grouping and are associated with occasional reactions.

In cases of acute nephritis in which oliguria exists and in which the serum protein is still normal or nearly normal it is well to eliminate salt from the diet. From 50 to 60 gm. of protein a day are given. Five hundred cubic centimeters of 20 per cent solution of glucose or 1,000 c.c. of a 10 per cent solution with an ampule of aminophylline (3¾ grains or 0.25 gm.) is usually helpful as a mild diuretic. Potassium nitrate may be given in these cases but it is not advisable to use mercurial diuretics unless a diuresis is already established.

In cases of cardiac disease with congestive failure it is highly important to rid the body of the offending substance; namely, the edema fluid, as frequently the lungs, liver and other tissues of the body are engorged with water. In cases of edema caused by cardiac failure, mercurial diuretics offer quicker and more complete relief in ridding the body of fluid than any other diuretic. They should not be given, however, in the presence of renal failure with uremia. The xanthine group offers effective therapeutic aid and in combination with the mercurial diuretics adds materially to our resources. Potassium nitrate also is a diuretic aid in these cases and can be employed effectively. From 500 to 1,000 c.c. of a 10 per cent solution of glucose with an ampule of aminophylline (3¾ grains or 0.25 gm.) is effective in many cases. It should be given slowly and if symptoms of pulmonary congestion occur, the injection should be discontinued. By the addition of an ampule of aminophylline (3¾ grains or 0.25 gm.) to the solution reactions are materially decreased in frequency and degree.

Digitalis has for many years held a prominent place in the treatment of congestive failure, especially in the long convalescent period. Its action should be closely watched and the physician should always be on guard for symptoms of toxicity, especially in the older individual.

In cases of hepatic cirrhosis excess fluid collects first in the abdominal cavity. Usually paracentesis is necessary repeatedly and the patient may require paracentesis once or twice a week. Usually hypoproteinemia does not exist. However, injections of 500 c.c. of a 6 per cent solution of acacia in 0.06 per cent solution of sodium chloride have seemed to increase diuresis

and slow down the accumulation of fluid in the abdominal cavity. A salt-free diet with an intake of 500 to 800 c.c. of fluid daily is advisable. Potassium nitrate, 6 to 9 gm. a day, has some diuretic effect. Operation is not of much value in these cases.

It is a good rule in any case of generalized edema to keep the intake of salt as low as possible, to try to restore the electrolytic and physical balance in the body, to restore as nearly as possible the normal function of the heart and kidneys and to eliminate the excess fluids retained in the body by the therapeutic measures of choice. Therapeutic measures which might produce reactions in the body should be avoided if possible.

M. W. BINGER

REVIEWS

Clinical Aspects of the Electrocardiogram. By HAROLD E. B. PARDEE, M.D. 434 pages; 24 × 16 cm. Paul B. Hoeber, Inc., New York. 1941. Price, $5.75.

The fourth edition of this book, which has been revised and enlarged, maintains the good standards set by previous editions. It is a comprehensive text on every aspect of clinical electrocardiography, and is strongly recommended to the cardiologist and internist. It can also be read with profit and interest by medical students, physiologists and others interested in electrocardiography. The author has devoted much space to a discussion of the normal and abnormal variations of the electrocardiogram, and even though there is a relative paucity of tracings pictured, it is evident that each is carefully chosen to reveal several deviations. The tracings are, for the most part, distinctly reproduced and each is followed by a brief descriptive analysis of the abnormal details. The author discusses controversial subjects, briefly states his own views, and supports them with statistical data compiled either by himself or other workers in this field.

A definitely worthy feature is the correlation of the clinical significance of axis deviation, abnormal waves and arrhythmias with anatomical, pathological and physiological investigations. This is particularly well done in the discussion of bundle-branch block, myocardial infarction, extrasystoles and heart block. One chapter is devoted to purely clinical features of the arrhythmias with specific reference to their origin, diagnosis and prognosis.

Only recently has there become apparent some unanimity of opinion concerning the evaluation of the different chest leads and the interpretation of their respective abnormal deviations. The author presents the current opinions with reference to these leads. He describes the chest leads and illustrates them with tracings together with each set of normal and abnormal standard leads, thus giving the reader a complete picture of the electrocardiogram. Detailed information is given concerning the nomenclature and terminology recommended by the American Heart Association and the Cardiac Society of Great Britain and Ireland.

The theories of the physiological and mathematical fundamentals are discussed in a chapter which, although very stimulating and instructive, is in places slightly confusing. Appendix I is concerned with methods of determination of electrocardiogram vector directions. The necessary tables and charts are given for their computation.

Each chapter is followed by a current, adequate bibliographical reference list arranged according to the various subjects discussed.

It is gratifying to note that the author's conception of the value of clinical electrocardiography includes a realization that this procedure has the same degree of limitation as any other single method of cardiac examination. This point is illustrated by the following quotations: "The decision as to the interpretation of the electrocardiographic changes must be made on clinical grounds." . . . "The electrocardiogram like any other single feature of the clinical examination is quite insufficient as an isolated fact to afford a basis for a prognosis."

E. T. L.

Williams' Obstetrics: A Textbook for the use of Students and Practitioners. Eighth edition. By HENRICUS J. STANDER, M.D., F.A.C.S. 1401 pages; 25 × 17.5 cm. D. Appleton-Century Company, New York. 1941. Price, $10.00.

While the traditional form and conservative teaching of "Williams' Obstetrics" have been retained, the author points out that: "The book has been almost completely rewritten, with the result that little of the original text remains unaltered." Com-

paring this eighth with the first edition, one finds startling differences in size and text which are the result of progress made in obstetrics during the 38 years intervening between the first and present editions. The first edition appeared in 1903 and contained 845 pages, 630 illustrations, and the index occupied 26 pages. The present edition published this year contains 1401 pages, 925 illustrations on 718 figures, while the index occupies 62 pages. Space in a brief review does not permit the interesting comparison of methods described in the two editions or even a list of new material added since the first appeared.

Since the seventh edition, three new chapters have been added covering the subjects of diseases and abnormalities of the newborn; classification of abnormal and contracted pelves; and sudden death and maternal mortality. This new edition is full and modern. The average medical student will probably welcome the shortening of the section on embryology. The new classification of the toxemias of pregnancy of the American Committee on Maternal Health has been used; and a new classification of contracted and abnormal pelves is proposed. Because of the length of this material on the pelvis, it is the opinion of the reviewer that the student will find it rather difficult to assimilate. Roentgen pelvimetry is discussed in detail. Newer operative technics are adequately described, and medical and surgical conditions complicating pregnancy are thoroughly discussed. Proper emphasis has been placed on chemotherapy in the treatment of urinary tract infections as well as in puerperal infection. The chapter dealing with amnesia, analgesia and anesthesia in labor admirably covers this field.

A welcome change from the older editions of this classic text has been the relegation of much of the theoretical considerations to small type. Historical material, while also presented in small type, has been retained and given its proper place.

The type is large, clear and easily readable. There is a large index for this large book. References to the literature, both historical and modern, are given at the end of each chapter. The publishers state that more than half of the illustrations are new. The work is profusely and excellently illustrated with drawings by Elizabeth Brödel, photographs and improved illustrations.

The author is to be congratulated upon the diligent way in which he has preserved the tradition of the work and the thoroughness with which it has been modernized. The resulting book remains one of the outstanding classics, for student and practitioner, in American obstetrics.

J. E. S.

Clinical and Experimental Investigations on the Genital Functions and Their Hormonal Regulation. By BERNHARD ZONDEK. 264 pages. Williams and Wilkins. Baltimore. 1941. Price, $4.50.

When a man as closely identified with the development of sex physiology as Bernhard Zondek writes a book on the subject it deserves careful study. The introduction clearly states the scope of the material covered as the author's own contributions to the field since 1935. These include work on the natural occurrence of estrogens, the effects of high doses of estrogens, the fate of sex hormones in the organism, and menstrual studies.

For one without a good background in sex physiology this book would be difficult to evaluate. The data are frequently insufficient to warrant the conclusions made, for the work of one man, especially when spread over many problems, is rarely adequate for establishing fundamental principles. Dr. Zondek runs into this difficulty particularly in the problems connected with the menstrual cycle, where arguments based on the rat are applied to the human with little consideration of the experimental work done in other laboratories on the monkey. Only a few clinical cases are presented in evidence.

Workers in this country will probably take greatest issue with the terminology. We like to think that the last 10 years have clarified the relations of the prolans to the pituitary principles and proved the identity of pseudomenstruation and menstruation. Zondek's terms synprolan for the pituitary synergist (generally considered in this country to be FSH) and prosylan as prolan plus synprolan imply more knowledge than we possess. According to this system FSH should be called prosylan A, although no one has described a synprolan A.

The work of the author, the content of some 85 published articles, is well summarized and in a convenient form for reference. Many of the ideas are stimulating, especially the author's theory of the mechanism of menstruation.

E. B.

Bacteriology in Neuropsychiatry. By NICHOLAS KOPELOFF, Ph.D. 316 pages; 15.5 × 23.5 cm. Charles C. Thomas, Springfield, Ill. 1941. Price, $4.50.

The author presents in this volume a survey of the literature relating to the bacteriologic and immunologic phase of neurology and psychiatry. The subject is considered under the following headings: diseases of known etiology with primary involvement of the nervous system; diseases of known etiology with secondary involvement of the nervous system; diseases of unknown etiology involving the central nervous system; and immunology of the central nervous system.

It is of value to have consolidated in a single volume the facts and problems of this extensive subject uncritically presented and interpreted. The book contains an extensive bibliography.

E. F. C.

COLLEGE NEWS NOTES

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Dr. Samuel Weiss, F.A.C.P., New York, N. Y.—1 reprint;
Dr. August A. Werner, F.A.C.P., St. Louis, Mo.—6 reprints.

Schedule of Examinations by Certifying Boards

The following Boards have announced schedules of their examinations as follows:

American Board of Internal Medicine:
William S. Middleton, M.D., Secretary
1301 University Ave.
Madison, Wis.

Written Examinations: October 20, 1941; February 16 and October 19, 1942.
Oral Examinations: St. Paul, April, 1942, in connection with meeting of the American College of Physicians; Atlantic City, June, 1942, in connection with meeting of the American Medical Association.

AMERICAN BOARD OF DERMATOLOGY AND SYPHILOLOGY: C. Guy Lane, M.D., Secretary 416 Marlboro St. Boston, Mass.	Written Examination: November 3, 1941. Oral Examination: December 12–13, 1941.
AMERICAN BOARD OF PEDIATRICS: C. A. Aldrich, M.D., Secretary 707 Fullerton Ave. Chicago, Ill.	Oral Examination: Boston, October 7–8, 1941, in connection with the meeting of the American Academy of Pediatrics.
AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY: Walter Freeman, M.D., Secretary 1028 Connecticut Ave., N. W. Washington, D. C.	Oral Examination: New York, December 19–20, 1941.

For further details and application forms communicate with the respective secretaries.

The Administrator of Veterans Affairs has established a Neuropsychiatric Research Unit at the Veterans Administration Facility, Northport, L. I., N. Y. The unit will operate as an integral part of the Medical and Hospital Service under the direction of Dr. Charles M. Griffith, F.A.C.P., Medical Director, and under the immediate supervision of Dr. Hugo Mella, F.A.C.P., Chief, Postgraduate Instruction and Medical Research Division, Medical and Hospital Service, Washington, D. C.

This unit will conduct clinical and laboratory research in connection with neuropsychiatric disabilities found among veterans. An effort will also be made to standardize diagnostic and therapeutic methods used in connection with the management of neuropsychiatric diseases and, from time to time, the personnel of the unit will be engaged in teaching modern concepts of neurology, psychiatry and neuropathology to medical officers of the Veterans Administration detailed for this purpose.

The National Gastroenterological Association has announced that its 7th Annual Spring Convention will be held in New York, N. Y., June 3–5, 1942.

The Pittsburgh Pediatric Society held its regular meeting in connection with a "pediatric clinic day" at the Windber Hospital, Windber, Pa., June 25, 1941. Dr. Hyman A. Slesinger, F.A.C.P., Windber, spoke on "Allergy in Childhood," and Dr. Elwood Stitzel, F.A.C.P., Altoona, Pa., spoke on "Schüller-Christian Disease."

The American Therapeutic Society held its 43rd Annual Meeting in Cleveland, Ohio, during June. At this meeting Dr. Harold S. Davidson, F.A.C.P., Atlantic City, N. J., was elected President; Dr. Francis D. Murphy, F.A.C.P., Milwaukee, Wis., and Dr. Euclid M. Smith, F.A.C.P., Hot Springs National Park, Ark., Vice Presidents; Dr. Oscar B. Hunter, F.A.C.P., Washington, D. C., Secretary; Dr. Daniel L. Sexton, F.A.C.P., St. Louis, Mo., Treasurer; and Dr. Francis M. Pottenger, Jr. (Associate), Monrovia, Calif., Editor.

Dr. Jonathan C. Meakins, F.A.C.P., Montreal, Que., Regent and former President of the College, has been appointed Dean of the Faculty of Medicine of McGill University. Dr. Meakins is also Professor of Medicine and Director of the Department at McGill University, Physician-in-Chief and Director of the University Clinic at the Royal Victoria Hospital.

Dr. Lowell Ashton Erf (Associate), formerly Instructor in Clinical Medicine, and Research Associate in the Crocker Radiation Laboratory of the University of California, has accepted an appointment with Jefferson Medical College of Philadelphia, beginning with the September, 1941, term.

Dr. William G. Leaman, Jr., F.A.C.P., Philadelphia, Pa., has been appointed clinical Associate Professor of Medicine at the Woman's Medical College of Pennsylvania and Visiting Physician at the Philadelphia General Hospital.

Dr. Samuel M. Feinberg, F.A.C.P., Chicago, Ill., has been elected to honorary membership in the Argentine Society for the Study of Allergy.

Dr. William R. Mathews, F.A.C.P., Shreveport, La., has been elected President of the Louisiana Association of Pathologists.

The American Federation for Clinical Research was organized at Atlantic City, N. J., May 5, 1941. Dr. Maurice A. Schnitker (Associate), Toledo, Ohio, was elected President, and Dr. Thomas M. Durant, F.A.C.P., Philadelphia, Pa., Secretary-Treasurer.

Dr. Logan Clendening, F.A.C.P., Kansas City, Mo., spoke on "Some Memorials of Medicine in America" at a recent meeting of the Hollywood (Calif.) Academy of Medicine.

Dr. Walter H. Baer (Associate), Manteno, Ill., has been elected President of the Illinois Psychiatric Society.

Dr. Philip F. Barbour, F.A.C.P., Louisville, Ky., was one of the guests of the Union County Medical Society who recently conducted a pediatric conference at Morganfield, Ky. Dr. Barbour discussed "Chronic Heart Disease" and "Diarrhea and Dysentery."

Dr. Maurice C. Pincoffs, F.A.C.P., Baltimore, Md., was elected one of the Vice Presidents of the Medical and Chirurgical Faculty of Maryland at its recent meeting in Baltimore.

Dr. Walter Lincoln Palmer, F.A.C.P., Chicago, Ill., spoke on "Diagnosis and Treatment of Gastric Disease" at the annual one-day clinic of the alumni of Wayne University College of Medicine.

Among the speakers at a conference on serology and syphilis control, held in Ann Arbor, Mich., sponsored by the American Association of Industrial Physicians and Surgeons, the U. S. Public Health Service, and the American Social Hygiene

Association, were: Dr. George H. Gehrmann, F.A.C.P., Wilmington, Del.; Dr. Udo J. Wile, F.A.C.P., Ann Arbor, Mich.; Dr. Walter M. Simpson, F.A.C.P., Dayton, Ohio; Dr. Otis L. Anderson, F.A.C.P., U. S. Public Health Service; and Dr. Charles Walter Clarke, F.A.C.P., Caldwell, N. J.

Dr. John A. McIntosh, F.A.C. P., San Antonio, has been elected one of the Vice Presidents of the Texas Neurological Society.

Dr. Dolph L. Curb, F.A.C.P., Houston, has been elected one of the Vice Presidents of the Texas Society of Gastro-Enterologists and Proctologists.

Dr. Charles T. Stone, F.A.C.P., Galveston, has been elected President of the Texas Heart Association, Dr. William B. Adamson, F.A.C.P., Abilene, Vice President, and Dr. Victor E. Schulze, F.A.C.P., San Angelo, was reëlected Secretary.

Dr. Carl J. Wiggers, F.A.C.P., Cleveland, Ohio, received the honorary degree of Doctor of Science from the University of Michigan at the Commencement, June 21, 1941.

The Washington State Medical Association held its 52nd Annual Meeting in Seattle, August 24–27, 1941. Among the speakers at this meeting were:

Dr. Edwin G. Bannick, F.A.C.P., Seattle—"General Status of Chemotherapy";
Dr. Lester J. Palmer, F.A.C.P., and Dr. George D. Capaccio (Associate), Seattle—"Present Day Insulins."

Dr. Andrew C. Ivy, F.A.C.P., has been elected President of the Chicago Society of Internal Medicine. Dr. Harold C. Lueth, F.A.C.P., Evanston, Ill., has been elected Vice President of the Society, and Dr. Richard B. Capps (Associate), Secretary-Treasurer.

Dr. David P. Barr, F.A.C.P., for a number of years Professor of Medicine at Washington University School of Medicine and Physician-in-Chief to the Barnes Hospital, St. Louis, has been appointed Professor of Medicine and Physician in Chief to New York Hospital. Dr. Barr succeeds Dr. Eugene F. Du Bois, F.A.C.P., who has been made Professor of Physiology and Head of the Department of Physiology and Biophysics.

The 3rd biennial Rocky Mountain Medical Conference was held at Canyon Hotel, Yellowstone National Park, September 2–4, 1941. Among the speakers at this meeting were:

Dr. Clarence M. Hyland, F.A.C.P., Los Angeles, Calif.—"Convalescent Human Serum Therapy; Serum and Plasma as Blood Substitutes";
Dr. James G. Carr, F.A.C.P., Chicago, Ill.—"Clinical Diagnosis of Coronary Occlusion" and "Cardiac Irregularities and Paroxysmal Tachycardia."

The Connecticut State Medical Society held its 17th Clinical Congress at New Haven, September 16–18, 1941. Among the guest speakers were:

Dr. Irvine H. Page (Associate), Indianapolis, Ind.—"Hypertension";
Dr. Samuel A. Levine, F.A.C.P., Boston, Mass.—"Modern Treatment of Congestive Heart Failure";
Dr. Burrill B. Crohn, F.A.C.P., New York, N. Y.—"Diagnosis and Treatment of Bleeding from the Stomach."

The Medical Society of the State of Pennsylvania will hold its 91st Annual Session in Pittsburgh, Pa., October 6–9, 1941. The meeting will consist of: morning general assemblies; round table conferences; afternoon section programs on Medicine, Surgery, Eye, Ear, Nose and Throat Diseases, Dermatology, Urology, Obstetrics and Gynecology, Pediatrics, and Clinical Laboratory Medicine; and scientific and technical exhibits. All physicians, residents of Pennsylvania and of adjacent states who are members of, or are eligible to membership in, a county medical society, are cordially invited to attend this meeting. There is no registration fee.

Among the out-of-state guest speakers will be:

Dr. Charles A. Waters, F.A.C.P., Baltimore, Md.—"Has Preoperative Irradiation a Place in the Treatment of Renal Tumors?";
Dr. Albert M. Snell, F.A.C.P., Rochester, Minn.—"Changing Conceptions of Portal Cirrhosis";
Dr. Edward J. Stieglitz, F.A.C.P., Garrett Park, Md.—"Problems of the Aging";
Dr. Charles A. Doan, F.A.C.P., Columbus, Ohio—"The More Common Blood Dyscrasias—Their Diagnosis and Treatment."

The Omaha Mid-West Clinical Society will hold its 9th Annual Assembly in Omaha, Nebr., October 27–31, 1941. Among the members of the College who will present papers at this meeting are: Dr. W. Osler Abbott (Associate), Philadelphia, Pa.; Dr. S. Bernard Wortis, F.A.C.P., New York, N. Y.; Dr. Byrl R. Kirklin, F.A.C.P., Rochester, Minn.; and Dr. Albert M. Snell, F.A.C.P., Rochester, Minn.

Lt. Commander Stanton Tice Allison, Medical Corps, U. S. N. R. (F.A.C.P.) has been appointed chief of medicine, U. S. Naval Hospital, Brooklyn, N. Y.

1942 Program of Intensive Postgraduate Courses Arranged by the American College of Physicians

The Advisory Committee on Postgraduate Courses, with the approval of the Committee on Educational Policy and the Executive Committee of the College, announces the following tentative program of postgraduate courses for the winter and spring of 1942. Some details are yet to be completed, but all the institutions mentioned have indicated a willingness to coöperate fully and many of the directors of courses are already outlining the courses and organizing their faculties.

This will be the fifth year of this activity by the College. The courses are organized especially for Fellows and Associates of the College, but where facilities are available, courses will be open to those with adequate preliminary training who are now preparing either to meet the requirements of membership in the College or certification by the American Board of Internal Medicine.

The courses are made available by the College to its members at minimum cost, because the College assumes full responsibility for promotion, advertising, printing and registration. The tuition will be $20.00 for each week. All tuition fees are paid in bulk sum to the institution or director and faculty of each course. Registrations will not be accepted until later in the year when the formal Post-graduate Bulletin and registration form have been distributed.

The program of courses has again been expanded to meet the growing popularity of these courses. Some of the courses will be given during February and others, at more convenient centers, just preceding the Annual Session of the College at St. Paul, Minn. (April 20–24, 1942).

Tentative Schedule of Courses

A. General Medicine

1. University of Minnesota Center for Continuation Study, Minneapolis.
   C. J. Watson, M.D., Professor of Medicine, *Director.*
   Two weeks, April 6–18, 1942. $40.00.
2. University of California Medical School and Stanford University School of Medicine, San Francisco.
   Directors to be announced.
   Two weeks, February 2–14, 1942. $40.00.

B. Allergy

1. The Roosevelt Hospital, New York City.
   Robert A. Cooke, M.D., *Director.*
   Two weeks, February 2–14, 1942. $40.00.
2. Washington University School of Medicine and Barnes Hospital, St. Louis.
   Harry L. Alexander, M.D., Professor of Clinical Medicine, *Director.*
   Two weeks, April 6–18, 1942. $40.00.

C. Cardiovascular Diseases

1. Peripheral Vascular Diseases.
   Mayo Foundation, University of Minnesota, and Mayo Clinic, Rochester.
   Edgar V. Allen, M.D., Associate Professor of Medicine, *Director.*
   Two weeks, April 6–18, 1942. $40.00.
2. Cardiovascular Disorders.
   Massachusetts General Hospital, Boston.
   Paul D. White, M.D., *Director.*
   Two weeks, February 2–14, 1942. $40.00.

D. Gastro-Intestinal Diseases

1. University of Pennsylvania Graduate School of Medicine, Philadelphia.
   Henry L. Bockus, M.D., Professor of Gastro-enterology, *Director.*
   One week, February 2–7, 1942. $20.00.
2. University of Chicago, School of Medicine, Chicago.
   Walter Palmer, M.D., Associate Professor of Medicine, *Director.*
   Two weeks, April 6–18, 1942. $40.00.

E. Arthritis and Rheumatism

Mayo Foundation, University of Minnesota, and Mayo Clinic, Rochester.
Philip S. Hench, M.D., Associate Professor of Medicine, *Director.*
One week, April 13–18, 1942. $20.00.

Other courses, including one in General Medicine of two weeks' length during February in the East, and one in Tuberculosis of one week during April in the West, are under consideration, and announcements will be made later.

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MASS IMMUNIZATION AGAINST TYPHUS FEVER*

By R. E. DYER, Senior Surgeon, U. S. Public Health Service†

IN the control of typhus fever we are faced with a problem presented by a disease which is transmitted in nature by two arthropod vectors of different genera. The epidemiological picture, based as it is on the arthropod-host relationship and feeding habits of the vectors, is divided into two types. One of these epidemiologic types, to which we usually refer as endemic typhus, is determined by the life history of the rat flea (*Xenopsylla cheopis*) and the second, or epidemic type, by the life history of the body louse (*Pediculus corporis*).

The rat flea acquires its infection in nature by feeding upon typhus-infected rats. As a result, this flea-borne, endemic, or murine typhus occurs especially in persons exposed on rat-infested premises and does not become epidemic except under conditions of heavy rat and flea concentration. The flea does not transmit this infection from man to man. Endemic typhus is present over large sections of the southern states, and, recently, has invaded some of the more northern states of the middle west. The incidence, although increasing, is yet relatively low, approximately 3,000 cases being recognized annually in this country. It is theoretically possible that this flea-borne typhus may become epidemic in character through the agency of the body louse. That has apparently not occurred in this country, possibly because body lice are relatively rare in the sections where endemic typhus is most prevalent, and because other factors seemingly necessary for typhus epidemic formation, such as war, famine, and concentrated human misery are lacking. Dependent as it is on a reservoir of typhus in the rodent population, the control of the endemic form of the disease rests with the control of the rodent population and the use of a specific immunizing agent would be largely limited to protection of those exposed especially in food handling establishments, warehouses, and like establishments which are apt to maintain rat harbors.

* Read at the Boston meeting of the American College of Physician, April 25, 1941.
† National Institute of Health, Bethesda, Maryland.

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An entirely different problem confronts us in the control of the epidemic or louse-borne type of typhus. This form of the disease has its reservoir in man. With the presence of body lice and a few cases of typhus, epidemics of the typhus may occur. The seriousness of these epidemics is directly proportional to the misery of the population attacked. In a well-organized population, with little overcrowding, louse-borne typhus is readily controlled by delousing measures and even without such measures would probably not cause the development of a typical typhus epidemic with the cases and deaths numbered by the thousands or by the millions as in Russia in the years 1920–22. However, the factors which favor the development of large typhus epidemics are the same factors which disorganize civil governments—war, famine, and civil revolution. Under such conditions civil organization breaks down and the carrying out of effective delousing measures becomes impossible. For this reason efforts have been made for many years by various workers to develop a vaccine. With the present conditions in large sections of the world operating for the increase of human misery and wretchedness which are the companions of typhus epidemics this seems an opportune time to review what we know of typhus vaccines.

The search for a typhus vaccine has followed two general lines: one has been based on the use of living virus, and the second has sought for the production of a killed vaccine. The French investigators have almost uniformly attempted to utilize the living agent as a vaccine while others have directed their efforts to the second method.

Live Virus Vaccines

Attempts have been made by various workers to use the living agent as a vaccine. In the first attempts epidemic strains of virus were used as in Nicolle's experiments.[1] In these he was able to produce an immunity in volunteers using blood serum from infected monkeys or the brains of infected guinea pigs as a source of virus. However, this did not prove a practicable method since the concentration of the virus varies with the animal and there is no feasible method of titrating that concentration prior to injection. The same difficulty was encountered by investigators who tried to prepare mixtures in which the virus was partially neutralized by convalescent serum. In vaccines of this sort there is always the danger of producing a typical, and possibly a severe, attack of the disease. As a result attempts along this line were largely dropped until the discovery of the milder endemic or murine type of the disease. Since this discovery two groups of French investigators, one headed by Laigret,[2, 3, 4, 5] the second by Blanc,[6, 7] have done a great deal of work with live vaccines made from murine typhus strains. There is little, if any, difference in the principles involved in the work of these two groups, the variations being in the technics used.

Laigret and his colleagues used a strain of endemic typhus and made preparations from the brains of typhus-infected guinea pigs. The etiologic

agent was found by them to retain its infectivity for more than three months if dried in egg yolk and stored at low temperatures. To modify the severity of the reaction they suspended this brain-egg yolk preparation in olive oil shortly before inoculating human beings. Recent work of Laigret and Durand has suggested that the infection in mice is somewhat more stable as regards virulence than the infection in guinea pigs and, further, that there is an increase in virulence for this species when passed by intracerebral inoculation. This suggests the possibility of the development of a fixed virus.

The second group attempting to utilize living material has employed first the tunica of guinea pigs infected with murine typhus and, more recently, the excreta of typhus-infected fleas. Blanc and his associates originally used a suspension of macerated guinea pig tunica taken shortly before the time of inoculation of subjects. To modify the severity of the infection they diluted the material 2,000 times and added sterile ox-bile to equal 5 per cent of the volume. The mixture was then allowed to stand for 15 minutes before use as a vaccine. One objection to this method was the difficulties encountered in preparing the vaccine shortly before use. This particular difficulty has been obviated by the more recent work of Blanc and Baltazard in which they have employed the excreta of typhus-infected fleas as a source of virus. They have found that when such excreta are dried the infection remains viable for approximately two years. Ox-bile is used as a medium for suspension just prior to inoculation, as was their method with the guinea pig tunica preparations.

Other investigators have attempted to produce mild typhus infections for the purpose of immunization by feeding infected material (Nicolle [8]) or by the instillation of such material on the conjunctivae (Sparrow [9]). In Nicolle's experiments he succeeded in producing mild but irregular infections in monkeys by feeding them the brains of infected guinea pigs. Sparrow used human volunteers and reported the production of a mild infection with subsequent immunity.

The laboratory experiments with the various modifications of live virus apparently justify the conclusion that an immunity can be established by this method. We can assume at least that living vaccines will produce a certain degree of immunity if infection with typhus follows the inoculation. The concentration of the infection in these vaccines is certainly so low that it can hardly be expected to produce an immunity without actual infection. The difficulties attendant upon these methods are inherent from the lack of a practical method of titrating the virulence of the vaccine or the resistance of the subject.

It is stated (Gaud [10]) in the reports on the vaccination of two million or more residents of North Africa that the reactions produced in natives are mild. Apparently the vaccination of Europeans is often followed by more severe reactions than usually seen in natives. This proved true in the only instance in which the use of live vaccine has been reported for the Western

hemisphere. The reports on the protection afforded the natives of North Africa against subsequent attacks of typhus are difficult to analyze since apparently no unvaccinated control group was set up, nor is it clear that those giving history of a previous attack of typhus were excluded from the experiment.

To summarize the work on live vaccines it may be stated that they probably produce an immunity commensurate with the severity of the reaction and that this immunity would be sufficient to aid materially in the control of a typhus epidemic. The reactions reported make it inadvisable to use such vaccine for the protection of Europeans or Americans if some safer method can be found.

Killed Vaccines

Before the successful cultivation of rickettsiae in tissue cultures the only sources of infected material from which a killed vaccine might be made were infected animals and infected arthropods, at that time—lice. The first attempts were made with infected animal tissues in which the infection was killed by heat or by some chemical. It was found that such preparations, made from tissues of animals infected by intraperitoneal inoculation, produced no immunity, probably due to the low concentration of virus in the animal tissues. Zinsser [11] succeeded in increasing the number of rickettsiae in rats by first injecting them with benzol and olive oil. Later he used vitamin-deficient guinea pigs or rats which had received preliminary roentgen-ray treatment. Rickettsiae were harvested from the peritoneal cavities of these animals and killed with formol. Suspensions of these killed rickettsiae were shown to produce immunity in guinea pigs and also in human volunteers (Varela [12]). The difficulties encountered in the production of rickettsiae by this method, although less than those encountered in the Weigl method (infra) did not give a great deal of encouragement in the problem of producing vaccine for mass immunization. A further step in the use of animals as a culture medium for rickettsiae was made by Castaneda.[13] He was able to produce large numbers of rickettsiae by the intranasal inoculation of rats and mice with infectious material from a strain of endemic virus. Such inoculations produced a rickettsial pneumonia in which the lungs of the animals showed great numbers of the organisms. Castaneda found that formalinized suspensions of these rickettsiae would protect guinea pigs and human volunteers against infectious doses of the homologous strain. Durand and associates [14, 15] have shown that Castaneda's method is applicable to epidemic strains. This method, though not without risk to the personnel of the manufacturing laboratory, is feasible for large-scale production of vaccine.

A second method of vaccine production utilized the intestines of the body louse as a living culture medium for the production of rickettsiae. Da Rocha-Lima,[16] noting that the concentration of virus in infected lice was higher than in human blood, used carbolized suspensions of naturally infected

lice to protect guinea pigs. Since he relied on lice infected by feeding on cases of typhus, the possibilities of vaccine production by this method were very limited. However, two years later Weigl [17] developed a technic for inoculating lice per rectum with suspensions of rickettsiae. Breinl [18] used Weigl's technic for the inoculation of lice and made a carbolized suspension of the infected louse intestines. He found that such suspensions afforded protection to guinea pigs. The technic of this method was improved further and has been used for the production of vaccine for human inoculations on a surprisingly large scale. Briefly, the Weigl method of vaccine production requires the injection of lice per rectum with suspensions of rickettsiae. The lice are then fed on immune individuals to secure multiplication of the rickettsiae. This period of feeding is followed by dissection of the lice and the removal of the intestines. These intestines, triturated in carbolized salt solution, constitute the vaccine. Roughly, it requires the intestines of 100 lice for enough vaccine to vaccinate one person. Weigl's vaccine has been used probably as extensively as the supply permitted and has apparently given a good degree of immunity against the disease. One report by Weigl may be cited [19] in which he states that of 2755 persons inoculated none developed typhus although all were later exposed. There are reports of cases where vaccinated individuals subsequently developed typhus, usually reported as mild, or modified, but on the whole it is the general opinion that Weigl's vaccine produces an immunity sufficient to control epidemics but probably neither an absolute nor a permanent immunity. When one considers the number of vaccinations necessary to immunize any large section of the population it becomes apparent that Weigl's method of preparation is too cumbersome to permit manufacture in sufficient quantities. However, enough of this vaccine probably could be produced to protect doctors, nurses, and orderlies engaged in the care of typhus cases during epidemics.

One other method has been developed for the cultivation of large numbers of rickettsiae in the production of vaccine. This method had its beginning in Nigg's [20] success in cultivating rickettsiae in tissue cultures. Kligler next cultivated a European typhus virus by using guinea pig tunica in normal saline and reported the protection of guinea pigs with a formalinized emulsion of these cultures. This was confirmed by Bengtson [22] who used Maitland's medium as a base. Zinsser [23] improved on this method by using a specially prepared agar on which the infected animal tissue was spread. At first Zinsser used material from guinea pigs as a source of inoculum but later, after the successful work of Barykine [24] and of Cox [25] in cultivating large numbers of rickettsiae in the yolk sac of the developing chick embryo he used similar cultures as a source for his inoculum.

Liu,[26] using Zinsser's method, reported an increase in the agglutinins for Proteus OX_{19} in inoculated individuals.

The Cox method of vaccine preparation is briefly as follows: Fertile eggs are incubated six to seven days; the inoculum is then injected into the yolk sac through a small hole in the air-sac end of the egg with a 1¼ inch

21-gauge needle. The eggs are then incubated until death of the embryo which usually occurs in five to seven days. The tissues are removed, washed in saline, pooled, and ground with alundum. The mixture is made up to a 10 per cent suspension, of saline containing formalin. Cox has shown that such a vaccine, made with an European strain of typhus, will effectively protect guinea pigs against the homologous strain.

Tchang,[27] using the Cox method with a " Chinese " strain of typhus virus, confirmed Cox's results on the production of immunity in guinea pigs. He stated further that 40 persons had been inoculated with this vaccine in Peking and that the final results would be reported later.

Kurotchkin and Wyckoff [28] made a comparative study of the Zinsser and Cox methods of vaccine production and found that the Cox vaccine was at least as effective an immunizing agent as the Zinsser vaccine and that this method gave also a more satisfactory answer to the question of cost and ease of quantity production.

Summary

Aside from vaccines made from living infectious material there are three methods of typhus vaccine production available: Weigl's louse intestine vaccine, Castaneda's mouse or rat lung vaccine, and Cox's yolk-sac vaccine. Zinsser's final method is apparently a modification of the Cox technic, is somewhat more difficult to prepare, and apparently does not produce any better immunity in guinea pigs. Weigl's vaccine, although it seems to produce a good degree of immunity, is too cumbersome for large scale production. The two remaining vaccines, those of Castaneda and of Cox, can be produced in quantity and, from available results on animals, give promise of producing an immunity in man. Experimentally, Castaneda's vaccine has been shown to protect man against subsequent inoculation with infectious material. The final answer on both vaccines awaits their use under controlled conditions in the presence of a typhus epidemic. Neither of these vaccines has been tried out adequately under such conditions although vaccine prepared by the Cox method is now on trial, in various countries where there is danger of epidemic typhus—Roumania, Hungary, Spain and China.

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CEREBRAL EMBOLISM IN MITRAL STENOSIS*

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THERE has been little investigation of the exact type of cardiac patient who is most likely to develop cerebral embolism. Likewise little attention has been paid to the immediate mortality and subsequent developments of such a cerebral complication. The purpose of this study is to analyze the data available in a group of cases of mitral stenosis that had clinical evidence of cerebral embolism. It is not the purpose to investigate cerebral embolism that occurs as a part of bacterial endocarditis nor is it our purpose to study the dislodgement of uninfected mural thrombi such as may appear following coronary thrombosis with myocardial infarction.[1] The latter problem has been studied recently [2, 3] and it was emphasized that sudden hemiplegia or so-called apoplectic strokes occurring in patients without hypertension are often misdiagnosed as instances of cerebral hemorrhage when in fact they are the result of embolism from a left ventricular mural thrombus after myocardial infarction.

In this present investigation cases were included only if there was clear cut evidence of mitral stenosis and clinical reason to believe that a rupture of a cerebral vessel had not occurred. It was not always possible to be certain of this latter point but in young or middle aged patients with little or no elevation of blood pressure we have assumed that a sudden cerebral accident was due to embolism. The validity of this assumption was enhanced by the fact that many of the cases showed evidence of embolism in other parts of the body and that about 25 per cent of the fatal cases were confirmed by postmortem examination. As evidence of gross cerebral accident only those cases were included in which sudden obvious paralysis occurred of one or more limbs, or of the face. In this way 48 cases were accumulated from the records of the Peter Bent Brigham Hospital and 24 cases from the private practice of one of us.

This survey was prompted by the clinical observation that many cases of mitral stenosis have a sudden cerebral embolism while otherwise in a fair state of cardiac compensation. It seemed that the typical case was one in which paralysis occurred suddenly at a time when there was no complaint of dyspnea and the patient was able to lie flat in bed, and had been ambulatory. In fact, it also seemed that after gross congestive failure had developed in patients with advanced mitral stenosis, although they might be observed over the course of years, cerebral embolism or hemiplegia was uncommon. It is well known that there are other antagonisms in clinical medicine in which the

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presence of one type of condition makes it unlikely that another will develop.[4] An example of this is the rarity of angina pectoris in the presence of persistent auricular fibrillation[5, 6] or the infrequency of the development of subacute bacterial endocarditis *after* congestive failure has taken place.[6, 7]

Of the 72 cases of mitral stenosis and cerebral embolism in this study, there were 26 males and 46 females. This is a slightly lower predominance of the female sex than occurs with mitral stenosis in general.[8] The average age of the entire group was 42.7 years, the range being from 18 to 65 years. Eighteen of the total number had hypertension and 54 did not. The average level of the hypertensives was 171 mm. of Hg systolic and 97 diastolic, the range being 155/75 to 230/130. Auricular fibrillation was present in 55 cases or 76.4 per cent of the series. Of these only three were transient fibrillators; in the others the arrhythmia was permanent. Although the exact time of onset of auricular fibrillation preceding the cerebral episode could not be ascertained in all cases, some data bearing on the point were available. Of the 55 cases of mitral stenosis and auricular fibrillation, in 26 instances persistent fibrillation was known to be present for varying times before the development of the embolism. Obviously the arrhythmia may well have been present for some time before the first observation. The duration of the observed fibrillation ranged from three days to nine years, with an average of 22 months. There were four instances in which it was known that the irregularity had been present no longer than 28, 14, 14, and three days. We have the impression that the cerebral accident is apt to occur during the early weeks or months after the onset of persistent auricular fibrillation. In a small number of instances, five, where the fibrillating state reverted to a normal rhythm either spontaneously or following quinidine therapy, embolism took place within a few hours or a day or two after regularization of the beat had taken place.*

It is noteworthy that in 17 instances (23.6 per cent) the rhythm was regular at the time the cerebral accident occurred and as far as could be ascertained fibrillation of the auricles had not taken place in the past. As would be expected the average age of the "regular" group was 3.9 years less than that of the "fibrillators." For some unexplained reason there was only one male among the 17 regular cases.

* When such a close relationship exists between a reversion to normal rhythm and development of embolism, it seems difficult to assume that the two events are coincidental.[9, 10, 11, 12, 13] It has been claimed[10] that embolism occurs as readily in fibrillating hearts on digitalis as on quinidine therapy. This conclusion not only seems untrue but the statistical evidence offered to support it contains an obvious arithmetical error. The fact that the same number of emboli occur in a consecutive group of patients with auricular fibrillation on quinidine therapy as in a control group on digitalis therapy cannot be interpreted in the sense that the two drugs are equally blameworthy. The average administration of digitalis in the control group continued over one or two years, whereas the quinidine was given only for several days. Expressed in other words, during 50,000 days of digitalis administration, two emboli may have occurred, while during but 500 days' use of quinidine two emboli also occurred. There can be no doubt that if a patient is fibrillating, is given quinidine, and within two or three days the heart rhythm becomes regular and a hemiplegia develops, the drug is the cause of the disaster. It is not inferred that embolism cannot occur in long-standing cases of fibrillation. In fact there was one instance in the group herein reported in which embolism took place nine years after the known onset of this arrhythmia.

An attempt was made to learn something about the progress of the paralysis that occurred in these cases. Unfortunately the data available did not include sufficient details to enable one to draw accurate estimates. It did seem fairly clear, however, that when improvement occurred, most of it was manifest within one month. In the recovered cases available for study, it was found that approximately one-third of the group with focal motor palsies demonstrated slight recovery of function in one year, whereas the remaining two-thirds showed no change. Despite the poor motor recovery, relatively few patients were bedridden after the embolism. In contrast to the poor prognosis for recovery of function in those with motor palsies of the extremities or face, clearing of speech disturbances occurred in practically all the patients who survived the embolism.

Cases in this study were also analyzed from the point of view of the presence or absence of congestive heart failure at the time of the cerebral embolism. We used as evidence of heart failure the presence of râles or fluid in the chest, engorged liver or peripheral pitting edema. Simple dyspnea without objective signs of congestion was not accepted as evidence of failure for purposes of this study. Although this is an artificial division it enabled us to compare those cases that were ambulatory and in a fair degree of cardiac compensation with those whose disease was more advanced. In this sense there were 49 without and 23 with heart failure. It is obvious that there is a time factor in the development of cerebral embolism from a left auricular mural thrombus and that it may be looked upon as an accident of heart disease. It is also clear that patients have mitral stenosis a much longer time without heart failure than with failure. If auricular thrombi develop early in the progress of rheumatic disease there would naturally be a longer opportunity for embolism to develop during the compensated than during the decompensated state. The difficulty is that the exact time that mural thrombosis develops in the course of mitral stenosis is not known. There is no method of predicting its presence except when embolic manifestations result. The large number of cases with a regular rhythm emphasizes the fact that auricular mural thrombosis does not require auricular fibrillation for its development in the presence of mitral stenosis. In fact one wonders whether auricular fibrillation has much additional importance in influencing thrombus formation. However, it is quite likely that dilatation of the auricles and diminished motion of the walls are factors. It is possible also that active carditis with injury to the endothelial lining may play a rôle in the formation of these clots.

An analysis was made of the effect of the presence of hypertension, and of the regularity or irregularity of the cardiac mechanism, and of heart failure on the subsequent course of events following cerebral embolism. In the entire series of 72 cases, there were 24 deaths occurring within a few days or a few weeks following the accident. This means that there is a 33 per cent immediate mortality in the average case of mitral stenosis that has cerebral embolism. The average time of death after the embolism was 4.3

days. In these cases it seemed fairly clear that embolic phenomena were the direct precipitating causes of the fatality. Fifteen additional cases died at varying times from one month to seven years following the accident, the average duration of survival in this group being 13.2 months. This indicates that after surviving the initial insult of a cerebral embolus these cases do not live on the average much longer than one year.

Among the 18 hypertensive cases, there were six immediate fatalities and four patients died subsequently, with an average period of 19.7 months of survival. In the 54 non-hypertensives, there were 18 immediate fatalities, and the average survival period of the 11 known to have died subsequently was 10.6 months. Thus it is clear that the pressure level has no influence on the immediate mortality in these cases. The greater survival period among the hypertensives is in accord with a previous study in which it was found that hypertension acts beneficially in cases of mitral stenosis.[7] The average age at the time of embolism in the hypertensive group was 47.5 years, while that in the non-hypertensives was 41.0 years. Heart failure was somewhat more frequent in the hypertensives than in those with normal pressure, i.e., nine out of 18 in contrast to 14 out of 54. Likewise auricular fibrillation was more common in the former group, i.e., 16 out of 18 in contrast to 39 out of 54. It seems therefore that patients with mitral stenosis and cerebral embolism who have hypertension are apt to be older, to have auricular fibrillation, to have congestive failure, and are likely to survive for a longer period than those not having hypertension.

A similar analysis was made of the rôle that auricular fibrillation might play in the progress of these cases. Of the entire 72 patients, 55 had auricular fibrillation and 17 had regular rhythm. Among the former there were 31 females and 24 males, whereas among the latter there were 16 females and only one male. The average age of the fibrillators was 43.5 years and of the non-fibrillators 39.6 years. There were 17 immediate fatalities among the former, and in the 14 of those dying subsequently the average survival period was 10.7 months. In the non-fibrillators, there were seven immediate fatalities and the only one known to have died subsequently lived four years. There was a greater incidence of hypertension among the fibrillators with mitral stenosis than in those with regular rhythm, there being 16 out of 55 in contrast to two out of 17. Similarly congestive failure was more common with (19 cases) than without auricular fibrillation (4 cases). It follows from the above survey that cases of mitral stenosis and cerebral embolism that have a regular rhythm are overwhelmingly of the female sex, that the fibrillators are older, have hypertension and congestive failure more frequently, but that the danger of an immediate fatality is not particularly influenced by the rhythm of the heart.

The last point that was investigated was the rôle that congestive heart failure might be playing in these cases. In the entire series of 72 cases, 23 had congestive failure and 49 had no failure. The average age of the two groups was 43.1 years and 42.3 years respectively. There was a much

greater immediate mortality among those with heart failure, i.e., 12 out of 23 cases as compared to 12 out of 49 cases without failure. The survival period of the six cases in the former group averaged 12 months and of the nine cases in the latter group averaged 14 months. As noted above hypertension was present more frequently in those with failure than in those who were compensated. It is of some interest that in all four instances where the rhythm was regular and congestive failure was present, "immediate mortalities" occurred, whereas in 13 regular cases without failure only four died. The obvious inference from the above data is that the presence of heart failure makes the immediate outlook more grave when cerebral embolism occurs in cases of mitral stenosis, especially when the rhythm is regular.

Discussion

Sterile peripheral emboli in cases of mitral stenosis occur as a result of dislodgement of bits of thrombi that are present in the left auricular wall. There is no known method of detecting the existence of mural thrombi until peripheral embolism takes place. Furthermore, there is no definite information that would enable us to estimate when mural thrombosis occurs on the auricular walls and therefore how soon after its formation embolism is most likely to result.

The similar problem concerning mural thrombosis in the ventricular cavity is much more clearly understood. Here the main cause is coronary thrombosis and ventricular infarction, the onset of which can be clearly defined. It is known that in the great majority of instances embolism from a ventricular thrombus takes place from a few days to a few weeks after the formation of the thrombus and only rarely months or years later. One cannot draw a close analogy between the possibilities that obtain when thrombi are present in the ventricles and in the auricles. In the former case the thrombi are apt to be very large and the ventricular contractions and movements very vigorous. In the auricles the thrombi are quite small and the contractions are comparatively weak. In fact there are crevices in the auricular appendages where the blood flow must be very sluggish and when auricular fibrillation is present there must be practically no contractions of the auricular wall. Furthermore, the rate of blood flow is different in the two chambers. Slowing of the blood stream is more conducive to the formation of clots whereas acceleration of the stream would tend to dislodge them. For these reasons the auricles, where the current is slow, should be the favorite site for the formation of thrombi. However, once such thrombi are present in the auricles, it is likely that they may remain silent a long time. Just the reverse set of circumstances exist in the ventricles.

It is clear from the above that the factors for the formation and dislodgement of thrombi in the auricles are numerous and difficult to analyze. The effect of auricular fibrillation, for instance, is open to some speculation. It is generally assumed that this arrhythmia enhances the likelihood of

thrombosis and embolism. The proof of this assumption is questionable. From this study it is evident that the average age of the cases that had auricular fibrillation and cerebral embolism was 3.9 years greater than those with regular rhythm. There was, therefore, a much longer period of time during which embolism could take place among the irregular than the regular cases. One might infer that it was not because of this arrhythmia but rather because of the increasing age and the longer period of time, that so many of the cases had auricular fibrillation. Furthermore, the large number of instances of embolism with regular rhythm indicates that thrombi can readily form in the auricles without fibrillation, and possibly even in those cases with fibrillation the thrombi may have formed earlier when the auricles were contracting normally.

Another unknown factor in the formation of auricular thrombi is the rôle of acute rheumatic carditis with the possible involvement of the endocardium. Because of the difficulty of detecting the presence or development of the thrombus until embolism results, it is difficult to ascertain the part played by infection and inflammation in this problem. Only when more is known about the mechanism of auricular thrombosis will it be possible to attempt methods of prevention such as the recent introduction of the use of heparin [14] might afford.

Summary

Seventy-two cases of mitral stenosis in which cerebral embolism occurred were studied.

There were 26 males and 46 females. The average age was 42.7 years.

There were 24 " immediate fatalities " among the entire 72 cases, i.e., 33 per cent mortality. The average period of survival of the 15 cases that died subsequently was 13.2 months.

Hypertension was present in 18 of the 72 cases. Hypertension had no effect on the " immediate mortality " but the survival period of those who recovered was distinctly longer (19.7 months). The average age of the hypertensives was 47.5 years and of the non-hypertensives 41.0 years. Heart failure and auricular fibrillation were more common in the hypertensive group.

Auricular fibrillation was present in 55 cases and regular rhythm in 17 cases. Among the latter there was only one male. The average duration of auricular fibrillation before embolism was 22 months. In five instances cerebral embolism occurred a few hours or a day or two after reversion to normal rhythm. The average age of the fibrillators was 43.5 years and of those with regular rhythm 39.6 years. The " immediate mortality " and the survival period of those recovering from embolism were not influenced materially by the presence of auricular fibrillation, despite the fact that hypertension and congestive failure were more common in this group.

There were 23 with and 49 without congestive heart failure. The former had a much greater " immediate mortality " (53 per cent as com-

pared to 24 per cent). In all four cases of congestive failure with regular rhythm "immediate fatalities" occurred, while among 13 regular cases without failure, only four died.

The prognosis for recovery of motor function after embolism was poor. Speech disturbance, however, cleared in practically all cases.

It seems that cerebral embolism is more likely to occur in cases of mitral stenosis that have very little objective evidence of congestive heart failure and is less apt to develop in those who are bedridden with advanced failure.

Cerebral embolism occurs more frequently in compensated than in decompensated cases of mitral stenosis because the former state lasts longer than the latter.

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PULMONARY INFARCTION IN HEART DISEASE*

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THE pathological changes of pulmonary infarction were known to Laennec, but he failed to recognize the relationship between embolism and infarction and called the condition "pulmonary apoplexy." Later, in 1856, Virchow pointed out the rôle of the embolus as the cause of lung infarcts. Over a period of many years numerous clinical, pathological, and experimental studies have established an accepted anatomical and clinical picture for pulmonary infarction. The typical pathological appearance of the lesion cannot be disputed. The necessary rôle of impaired pulmonary circulation in the development of the disease is also well established. The well known clinical syndrome seems sufficiently clear and generally is adequate to make the diagnosis of moderate-sized lesions which have been induced by emboli from surgical phlebitis. Observations at the necropsy table, however, have shown that patients with non-surgical diseases, like heart disease, frequently have extensive infarction of the lung that was not discovered during life. This fact stimulated the present survey of necropsy and clinical records from the Department of Pathology of Northwestern University, made available through the courtesy of Dr. James P. Simonds. The material was particularly well suited to a study of this kind because the records were compiled from four hospitals which represented such types as the large charity hospital, the private teaching hospital and one not affiliated with a university.

RESULTS

The survey covering 1311 necropsies performed in a six-year period revealed 101 cases with gross pulmonary infarction. The incidence (7.7 per cent) is similar to that reported by others. An extensive review by Hosai [1] revealed an incidence which varied from 0.65 per cent to 14.5 per cent.

Heart disease, the principal cause of death in 234 cases, was accompanied by gross pulmonary infarction 81 times (35 per cent), and yet a clinical diagnosis of pulmonary infarction was made only twice. This striking diagnostic failure prompted an analysis of the clinical symptoms and signs presented by these patients. As controls the patients with heart disease having no infarction were similarly analyzed. The results, compared in the tables, at once explain the high incidence of diagnostic failures. Symptoms thought of as characteristic of pulmonary infarction can also be explained as symptoms of heart failure. Patients presenting symptoms of hemoptysis, pleural pain, cough, dyspnea, cyanosis, fever, percussion dull-

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ness or pulmonary râles have received a diagnosis of heart failure rather than pulmonary infarct.

An analysis of symptoms and signs of both groups reveals only minor differences, with the exception of hemoptysis which occurs in 35 per cent of

TABLE I

Autopsy Incidence of Pulmonary Infarction
(1931 to 1939)

Number of autopsies reviewed	1311
Patients dying of heart disease	234
Number of patients with pulmonary infarction	101
Cause of infarction: Heart disease	81
Non cardiac	20
Clinical diagnosis of infarction (heart cases)	2

TABLE II

Necropsy Incidence of Pulmonary Infarction in Etiological Types of Heart Disease

	Number of Cases	Incidence of Infarcts	Incidence Per Cent
Hypertensive or arteriosclerosis*	161	48	30
Rheumatic type	33	12	36
Syphilitic	15	5	33
Bacterial	16	10	62
Congenital	1	0	0
Combined syphilis and arteriosclerosis	77	5	71
Combined rheumatic and arteriosclerosis	1	1	100
Total cases	234	81	34

* 19 of this group had coronary thrombosis

TABLE III

Comparative Frequency of Symptoms in Patients Dying of Heart Disease

	With Pulmonary Infarction			With No Pulmonary Infarction		
	Total Cases	With Symptoms	% Incidence of Symptom	Total Cases	With Symptoms	% Incidence of Symptom
Hemoptysis	81	29	35%	161	12	8%
Pleural pain	81	13	16	161	14	9
Precordial pain	81	37	46	161	65	42
Cough	81	33	41	161	84	54
Shock or sudden death	81	10	12	161	30	19
Dyspnea	81	78	96	161	145	95
Asthmatic attacks	81	6	7	161	9	6

the patients who had infarction, whereas it occurred in only 8 per cent of the others. Studies of the quantity of blood expectorated might reveal even greater differences, but such information was not available. Observations on a small number of patients of the series point to persistent recurrent hemoptysis as a distinctive feature of the disease. A comparison of the incidence of pain, cough, dyspnea, symptoms of shock, cyanosis, fever, signs

of consolidation, signs of heart failure, and auricular fibrillation reveals no significant variation in the two groups. Table 2 shows the incidence of pulmonary infarction in the various etiologic types of heart disease. Although a higher incidence is present in bacterial endocarditis there is no essential difference in the rheumatic, vascular or syphilitic groups.

TABLE IV

Comparative Frequency of Physical Findings with Pulmonary Infarction

	Total Cases	With Finding	% Incidence of Finding	Total Cases	With Finding	% Incidence of Finding
Cyanosis	81	48	62	161	80	50
Fever	81	39*	48	161	52†	33
Signs of pulmonary consolidation	81	21	25	161	30	19
Signs of congestive heart failure	81	71	87	161	154	94
Auricular fibrillation	81	29	36	161	53	35

* 8 of this group had pneumonia.
† 29 of this group had pneumonia.
No accurate data on friction rub.

TABLE V

Location of Infarct

Single Lobe Involvement	(43%)	Multiple Lobe Involvement	(57%)
	%		%
Right lower	23	Right upper	21
Right upper	2	Right lower	50
Right middle	1	Right middle	17
Left lower	15	Left upper	22
Left upper	2	Left lower	46

COMMENT

The infrequency of a clinical diagnosis of pulmonary infarction in this series is striking. Texts and articles dealing with this subject present the following clinical picture. Emboli large enough to occlude the pulmonary artery or main branches cause a symptom complex characterized by hemoptysis, marked dyspnea, cyanosis, substernal oppression and peripheral circulatory collapse (weak pulse, profuse sweating, ashen pallor, lowered blood pressure). This picture is mistaken sometimes for coronary thrombosis, but generally is sufficiently distinctive, even if heart disease is present, to lead to a correct diagnosis; moderate sized emboli which occlude secondary and tertiary radicles of the pulmonary artery produce hemorrhagic infarcts and a syndrome characterized by sharp pleuritic pain in the lower chest, dyspnea, hemoptysis, mental anxiety, mild degree of shock, increase in pulse rate, fever, signs of pulmonary consolidation, râles, and a friction rub. Although this picture is typical of postoperative emboli, it is inadequate for diagnosis of moderate sized emboli in patients with heart failure. The discrepancy in clinical manifestations of the same process, when it occurs in

different diseases, can be explained by differences in associated pathological changes in the lung. Passive hyperemia, pulmonary edema, brown induration, pulmonary fibrosis, pleural effusion or emphysema may coexist. In every subject of this series one or more additional disease processes were associated with infarction. Frequently a single subject showed passive hyperemia, emphysema, bronchopneumonia and pleural effusion. Any of the disease processes may inhibit symptoms which the embolus in a normal lung is capable of producing. In particular the shock and pleuritic pain might well be diminished through damage to the nerve receptors by long standing passive congestion.

The other signs, such as dullness, cyanosis, friction rub or fever, if present, might be interpreted as a sign of some phase of heart failure.

It is, therefore, apparent that this important disease process, frequently causing consolidation in one or all lobes of the lung in patients with heart disease and capable of precipitating heart failure or delaying recovery, has no characteristic clinical syndrome in the presence of heart disease. Symptoms and signs are not reliable aids because they can be produced by other manifestations of the decompensated heart. As an aid in this diagnostic dilemma the following suggestions are made. In the management of heart disease the high incidence of this complication should be kept in mind; infarction of the lung should be considered if the patient has persistent or recurrent hemoptysis, persistent deep cyanosis, unexplained jaundice, unexplained fever or sudden onset of heart failure not explained by overexertion or infection. Finally, critical analysis of the roentgen-ray films of proved cases may lead to the establishment of typical roentgen-ray findings for this condition.

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THE CHEMISTRY OF VITAMIN K*

By Louis F. Fieser, Ph.D., *Cambridge, Massachusetts*

In the following paper such aspects of the chemistry of vitamin K are surveyed as have a direct bearing on the present and future status of the use of this vitamin factor in practical therapy. The vitamin has proved very efficacious in the limited but important field of the treatment of hypoprothrombinemia associated chiefly with obstructions of the biliary tract and with the bleeding tendency of the newborn. The possibility of the uncovering of other clinical applications should not be overlooked.

Following Dam's discovery of the existence of a dietary antihemorrhagic factor in 1929,[1] a brief period of a few months in 1939 saw the isolation of pure vitamin K_1 from alfalfa,[2,3] the elucidation of the chemical formula of the substance [4,5] and its preparation by synthesis.[6,7] Too little time has as yet elapsed for the general recognition that certain of the conjectures tentatively advanced in the early stages of the work have now been discarded, and that some of the early reports concerning the antihemorrhagic activity of synthetic compounds were invalidated by imperfections in the technic of the bio-assay. The situation has been confusing to the extent that even clinicians interested in vitamin K therapy have been among those to fall prey to some of the current misconceptions. One is that the family of K-vitamins includes a whole host of individual substances. Actually the known list of natural antihemorrhagic factors includes only vitamin K_1, from alfalfa, and vitamin K_2, from putrefied fish meal. Vitamin K_1 is 2-methyl-3-phytyl-1, 4-naphthoquinone, and vitamin K_2 probably is 2-methyl-3-difarnesyl-1, 4-naphthoquinone.[8] The two substances are closely related in chemical structure, for they have the identical quinone nucleus and each possesses a long side-chain made up of the same, branched, five-carbon units (figure 1).

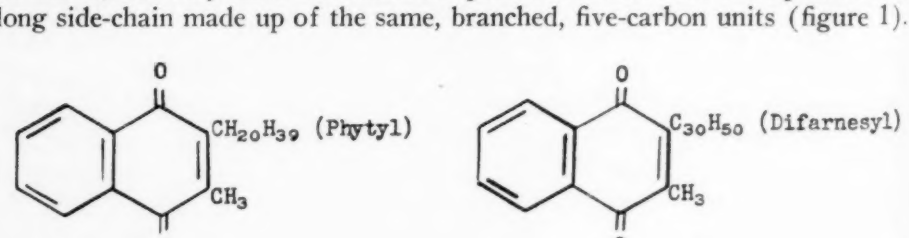


Fig. 1. Structures of the vitamins.

* Read at the Boston meeting of the American College of Physicians, April 23, 1941.

They constitute two members of a series which may well include additional representatives, for example with similar side-chains having 10 and 15 carbon atoms, but such substances have not as yet been encountered in nature. Vitamin K_1 alone has been produced synthetically. Fortunately, a comparatively simple method is available for the production of the compound in a pure form from methylnaphthohydroquinone and phytol.[6] Thus pure, synthetic 2-methyl-3-phytyl-1,4-naphthoquinone, which is identical in every respect with natural vitamin K_1 isolated from alfalfa, is the only true vitamin factor available for use as a therapeutic agent.

Another common misconception is that significant vitamin K activity is exhibited by a large number of simple quinones. Much depends upon what is considered to be " significant activity," but I should say that a substance to merit any consideration as a possible therapeutic agent certainly should possess at least one twenty-fifth the activity of vitamin K_1. Among a large number of quinones of diversified types which have been investigated, this criterion is met by only a very small group of naphthoquinones derived from or related to vitamins K_1 and K_2. The early note by Almquist and Klose [9] announcing that phthiocol possesses antihemorrhagic activity was justly acclaimed as an interesting discovery, for this was the first indication that substances other than the natural vitamins can exhibit this type of biological property. At present, however, it is recognized that phthiocol possesses only very feeble activity, being no more than about one five-hundredth as active as vitamin K_1,[10] and the substance has been dropped from consideration as a possible drug. The list of quinones possessing significant activity, as defined above, includes only the actual vitamins and their immediate derivatives, 2-methyl-1,4-naphthoquinone, which represents a component part of the vitamin K_1 and K_2 molecules, and three substances differing from vitamin K_1 only in having, in place of the phytyl group, the comparable but shorter hydrocarbon substituents farnesyl, geranyl, and cinnamyl.[10]

Indeed, contrary to preliminary indications, a high degree of specificity exists in the chemical structures of the natural vitamins. This can be seen from an inspection of the chart in figure 2, which summarizes some of the data accumulated in a comprehensive investigation of the relationship between vitamin K activity and structure.[10] By suitable processes of synthesis or of chemical transformation, about every conceivable modification of the vitamin K_1 molecule has been investigated, and in every instance the change is attended with a distinct diminution in biological potency. Such slight alteration as the addition of two hydrogen atoms, which changes the molecular weight only from 451 to 453, results in a 4- to 8-fold loss, depending on where the hydrogens are attached, while the addition of a CH_3 group, which changes the molecular weight by only 3 per cent, practically or wholly deactivates the molecule.

2-Methyl-1,4-naphthoquinone appears to constitute a single exception, for it is a highly active quinone [11] and yet, in contrast to the vitamins, which have at the 3-position a side-chain which is highly specific with respect to

length, branching, and unsaturation, it carries no side-chain at all at this position. Furthermore, the simple substance is found by the chick-assay method to be about three times as potent as vitamin K_1, at least on a weight basis. It is possible that Nature for once has been outdone, and that a simple substance obtainable merely by oxidizing one of the hydrocarbons found in coal tar is, *per se,* superior in potency to a vitamin factor produced by plant synthesis and provided with the elaborate phytyl chain derived from chlorophyll. I think not, and until the question can be settled experimentally, I favor the alternate explanation [6] that the methylnaphthoquinone administered merely provides one component required for a biosynthesis of an active compound of the true vitamin type. If the material is administered in such a way that it finds its way to the gut, combination might occur with

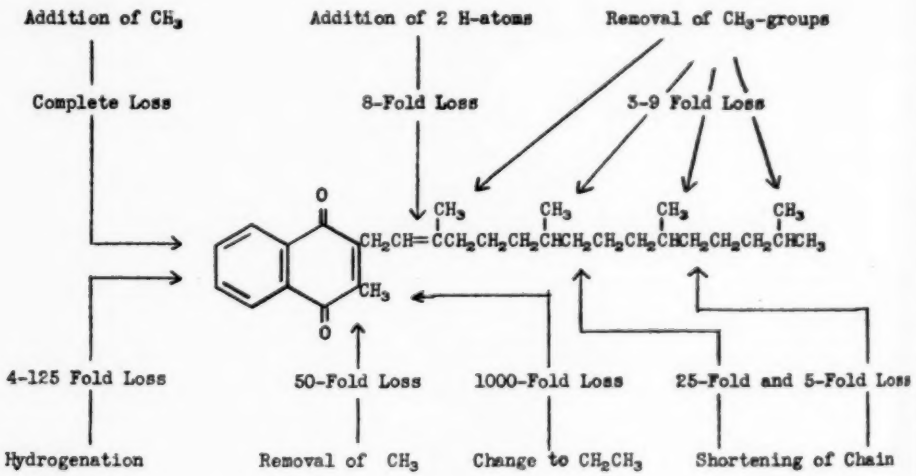


FIG. 2. Specificity of the vitamin K_1 structure. Loss in activity attending alterations in the vitamin K_1 molecule.

phytol to give vitamin K_1 while similar substances might well arise from a synthesis occurring in the liver utilizing vitamin A or a carotinoid pigment. Such a biosynthesis, which would entail a 3- or 4-fold increase in the molecular weight, would account for the anomalously high potency of the simple compound on a weight basis in the chick test. Further possible courses of the biosynthesis will be mentioned below.

I should like to dwell on the question of what happens to the administered material, because I think that this may be not merely a matter of academic interest but one which has a direct bearing on the choice of drugs for hypoprothrombinemia therapy. Although a rather confusing array of individual substances has been proposed, the choice really lies between one or the other of just two types. One of these comprises synthetic vitamin K_1, its oxide,[20] and hydroquinone diphosphate,[10] and possibly the analogous 2,3-disubstituted

naphthoquinone described below; the other is that of 2-methyl-1,4-naphthoquinone and its derivatives and congeners. Some of the substances of the second type are illustrated in figure 3. The reduced form, or hydroquinone, is too sensitive to oxidation to be used as such, but it can be employed as the water-soluble diphosphate [12] or disuccinate.[13] A water-soluble sodium bisulfite complex of unknown structure [14] is also active. The methylnaphthol [10] and methylaminonaphthol [15, 18] shown in the formulas probably undergo bio-oxidation to methylnaphthoquinone. The hydroquinone diphosphate and disuccinate likewise are probably transformed into the quinone in the organism.

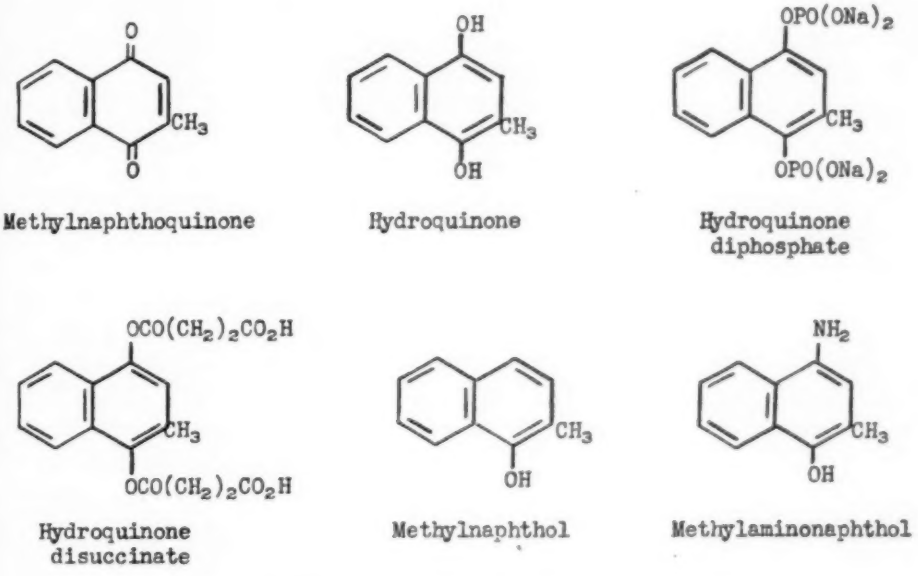


FIG. 3. 2-Methyl-1,4-naphthoquinone and related compounds.

Since each series apparently comprises a group of biologically equivalent individual derivatives, the question of prime importance in the selection of a preferred drug resolves itself into a choice between synthetic vitamin K_1 and methylnaphthoquinone. Other things being equal, it would seem reasonable to give preference to a substance identical with a natural vitamin. Certain purveyors of pharmaceutical products have confused the issue for the physician by offering methylnaphthoquinone under the designation "synthetic vitamin K." This is entirely false. Methylnaphthoquinone is a substitute compound, but it certainly merits consideration as such if it is capable of giving good service. This is the question which I should like to consider in more detail.

One disadvantage of methylnaphthoquinone is that it possesses a certain toxicity not encountered in the vitamin. When given orally to rats and mice,

methylnaphthoquinone is lethal at dosages of 0.35–0.5 g. per kg., whereas vitamin K_1 shows no lethal effect even in amounts up to 25 g. per kg.[16] The toxic dose of the substitute compound assuredly is so far removed from the therapeutic dose that no actual danger is likely to be involved in its use, but, nevertheless, the toxic character is a definite disadvantage. Those who have worked much with the compounds in the chemical laboratory are well aware that methylnaphthoquinone is a skin irritant while vitamin K_1 is entirely innocuous. Methylnaphthohydroquinone is a notable sternutator.

The fact that methylnaphthoquinone is more potent than vitamin K_1 in the chick assay might at first appear to constitute an advantage for the substitute compound. The relative responses evoked by the two substances in chicks, however, afford no adequate basis for predicting the ratio of effectiveness to humans. Many examples exist of a profound differential in the response of different species to different compounds (e.g., vitamin D_3 and calciferol given to chickens, rats and humans; testosterone and androsterone in the capon and rat assays). Certainly the results of animal experiments with drugs cannot be translated directly in terms of human therapy. The question of the relative therapeutic efficacy of the two agents is a matter for clinical investigation. Results of careful clinical comparisons made by Seligman, Hurwitz, Frank and Davis [17] indicate that no great disparity exists in the weight of vitamin K_1 and methylnaphthoquinone required to produce a satisfactory therapeutic response. It is by no means necessary or advisable to triple the dose of vitamin K_1 over that of the simple quinone merely on the basis of chick assays conducted with a standardized 18-hour period of observation. Indeed Seligman and co-workers find that vitamin K_1 has such a persistent and prolonged action that a single small dose is adequate for the treatment of even severe cases of hypoprothrombinemia and may well do the work of repeated dosage with other agents. From direct comparisons of several compounds, they conclude that "a single 10-milligram dose of vitamin K_1 given intravenously in cases of obstructive jaundice and biliary fistula produced a more rapid and prolonged effect than any other substance so far reported."

The strikingly contrasting chemical properties of vitamin K_1 and methylnaphthoquinone afford an interesting interpretation of the persistence and lack of toxicity of the former agent, as compared with the latter. Vitamin K_1 may be characterized as a stable, chemically inert substance, whereas methylnaphthoquinone is extremely reactive and tends to combine with a wide variety of reagents. The difference is understandable chemically, for methylnaphthoquinone has a free 3-position with a hydrogen atom capable of being replaced by substituents; in vitamin K_1 this position is blocked by the long phytyl group, which thus has a protective function. The contrast is clearly demonstrated by adding a solution of ethyl cyanoacetate in alcoholic ammonia to dilute solutions of methylnaphthoquinone and vitamin K_1, when a striking, deep blue color is produced in the former case and no change oc-

curs in the latter. The reagent used, to be sure, is quite foreign to the body, and this test is merely illustrative of a contrast in the properties. However, substances of the same type as ethyl cyanoacetate occur in the body and conceivably may combine with administered methylnaphthoquinone. One such substance is acetoacetic acid, which arises in the organism as a product of β-oxidation, and a test shows that this compound, in the form of the ester, gives a marked color reaction with methylnaphthoquinone but not with vitamin K_1 (table 1). Pyruvic acid, another biological product which

TABLE I

Color Reactions

(Tests made with 5 c.c. portions of 0.5 per cent solutions)

Reagent added	Color (after 2 days) 2-Methyl-1,4-naphthoquinone	Vitamin K_1
None	Light yellow	Light yellow
Ethyl cyanoacetate [1]	Intense blue (rapid)→brown	No change
Ethyl acetoacetate [1]	Deep red-brown	No change
Pyruvic acid [1]	Red-brown	No change
Aniline [2] (1 drop)	Orange-red	No change
Ethanolamine (1 drop)	Brown→deep red	Sl. brownish
Lysine [3]	Light orange-brown (slow)	No change
Thioglycollic acid (1 drop)	Deep yellow	No change
Cysteine [4]	Deep cherry red (rapid)	No change

[1] One drop of reagent, in a solution of 1.5 c.c. of alcohol and 0.5 c.c. of concentrated ammonia solution. This amount of alcoholic ammonia itself produces a discoloration, but the color change is considerably slower and much less intense than that arising in the presence of the reagent indicated. An improved test reagent for the detection of methylnaphthoquinone is prepared by dissolving 200 mg. of anhydrous sodium acetate in 1 c.c. of water and adding 9 c.c. of 95 per cent alcohol and 0.2 c.c. of ethyl cyanoacetate. When 0.5 c.c. of this reagent solution is added to 5 c.c. of an alcoholic solution of methylnaphthoquinone, a clear and persistent blue color appears and reaches maximum intensity in one-half to one hour. A faint but distinct color is observable in a solution containing 10 γ of methylnaphthoquinone per c.c.

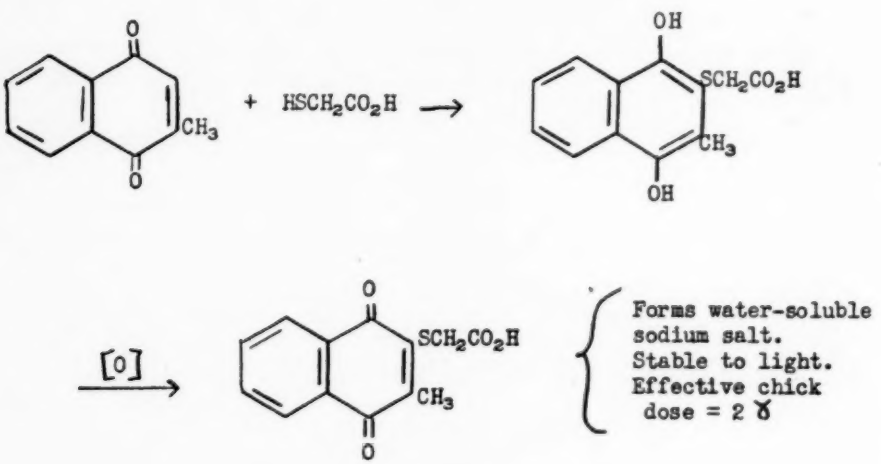
[2] The color reaction with dinitrophenylhydrazine described by Novelli (Science, 1941, xciii, 357) is applicable to 2-methyl-1,4-naphthoquinone but not, as this author implies, to vitamin K_1. I have made trials with a large amount of the vitamin and an extended period of heating, with only negative results.

[3] An aqueous solution of 44 mg. of lysine dihydrochloride and two equivalents of sodium acetate, diluted to 4 c.c. with alcohol.

[4] A solution of 100 mg. of cysteine hydrochloride and 50 mg. of sodium acetate in 5 c.c. of water was diluted with 15 c.c. of alcohol and the solution filtered from precipitated salt; 2 c.c. of this filtrate were used in each test.

also may be described as an active-hydrogen keto acid, gives a similar response. It is interesting to inquire into the possibility of other combinations in the body. Methylnaphthoquinone, in contrast to vitamin K_1 combines readily with amines foreign to the organism, such as aniline, and it also reacts with ethanolamine, the parent substance of choline. A slow but distinct reaction is noted with the amino acid lysine, probably due to a combination involving the ϵ-amino group, and this indicates the possibility that the administered quinone may combine similarly with the lysine units of proteins.

A still more striking and rapid reaction occurs with sulfhydryl compounds, of which thioglycollic acid constitutes a non-biological model. The reaction has been studied in our laboratory [18] and found to proceed readily and to yield a beautifully crystalline product (figure 4). The compound is almost as active in the chick assay as vitamin K_1, it is even more stable than this substance, its sodium salt is water soluble, and indeed the compound offers promise of being a valuable therapeutic agent. A similarly rapid reaction occurs with the natural amino acid cysteine, giving a highly pigmented product which is under investigation. One would expect glutathione to behave similarly. In consideration of the rapidity of the reaction, as compared with that with lysine, it is likely that methylnaphthoquinone can



2-Methyl-1,4-naphthoquinone-3-thioglycollic acid

FIG. 4. Reaction with a sulfhydryl acid.

combine with proteins most readily by utilization of the sulfhydryl groups rather than the ϵ-amino groups.

In view of this array of reactions which can occur under mild conditions, it seems hardly possible that methylnaphthoquinone administered to the animal body can escape some form or forms of alteration. Some of the possible transformations are indicated in figure 5. As mentioned above, the possibility exists that some of the material may combine with an alcohol of the phytol or vitamin A type, and afford a product of the actual vitamin K type. At the other extreme, it may in part undergo hydroxylation to phthiocol, for this reaction is easily realized in the laboratory.[19] Since this product is but feebly active, such a process would entail an effective diversion of the therapeutic agent. The result of the other possible transformations cannot be evaluated, for not enough is known about the properties of the possible

products. The fact that the thioglycollic acid derivative mentioned above is highly active suggests that at least some of the products of the reaction of methylnaphthoquinone with natural amino acids may possess antihemorrhagic activity.

This picture is not very favorable to the use of methylnaphthoquinone in therapy. The substance evidently can enter into some of the favorable forms of transformation, but the extent to which dissipating side reactions also occur remains in question. Consideration also should be given to the possible toxic, or otherwise undesirable, characteristics which may be associated with conjugates resulting from administered methylnaphthoquinone. The fate and action of the administered material would appear to be subject

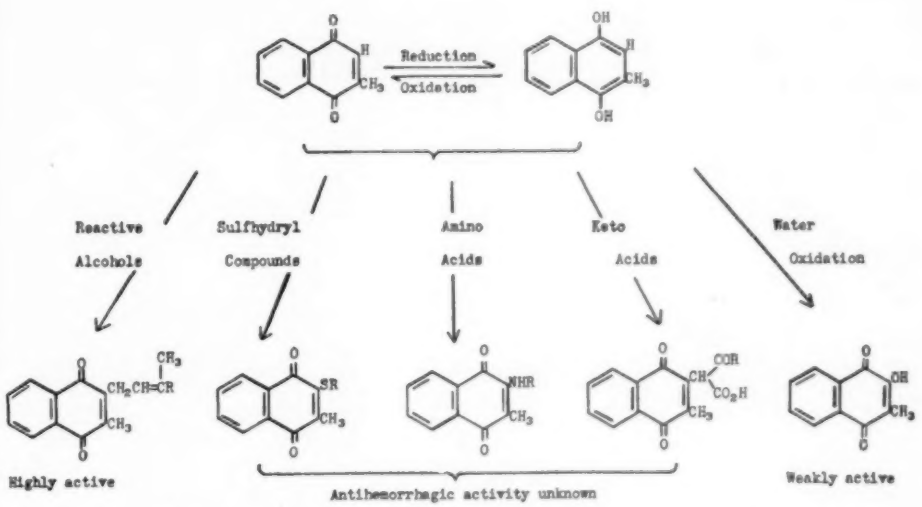


FIG. 5. Possible transformations of methylnaphthoquinone in the body.

to considerable uncertainty, and the wide opportunity for transformations of different types would lead one to expect a variability in the response, dependent upon the site and mode of administration and the condition of the patient.

These chemical considerations, which coincide with clinical findings, indicate that the stable, unreactive vitamin K_1 is a safer and surer agent for hypoprothrombinemia therapy, and one capable of persisting and exercising control over a prolonged period. The only precaution necessary in employing vitamin K_1 is to avoid exposure to light, for the substance is highly photosensitive, a property shared with methylnaphthoquinone. The sensitivity to light necessitates careful handling of the vitamin and is a definite if not a prohibitive disadvantage to its use as a drug. Fortunately this one defect can be obviated by using in place of synthetic vitamin K_1 an oxide derivative which appears to be biologically equivalent to the vitamin and

which is easily obtainable from and convertible into this substance. Vitamin K_1 oxide [20] is a colorless, or very nearly colorless oil, which, like the yellow vitamin, is soluble in alcohol and insoluble in water (figure 6). It shows no particular sensitivity to ordinary light, either alone or in solution, and requires no special handling. The oxide is even more stable and inert chemically than the parent vitamin. In the chick assay the oxide and vitamin are practically indistinguishable in antihemorrhagic activity, and Drs. Seligman, Hurwitz and Frank have informed me that they have obtained excellent clinical results with vitamin K_1 oxide.

Considerable interest has centered around the use in parenteral therapy of the various water-soluble derivatives of methylnaphthohydroquinone of the types mentioned above. However, the water-insoluble vitamin K_1 can be given satisfactorily, and indeed very effectively, in the form of an aqueous emulsion, with retention of all of the advantages noted. The remarkable dispersive quality of vitamin K_1 was observed by Dr. A. M. Seligman and

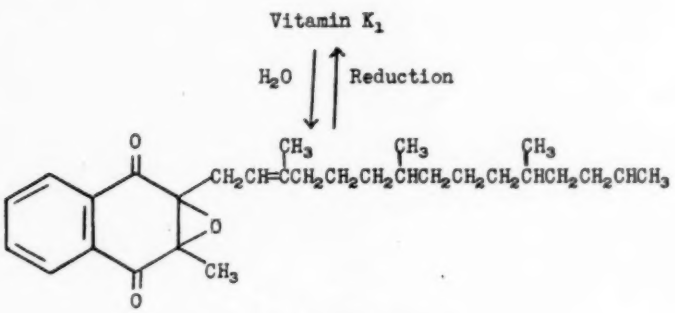


FIG. 6. Vitamin K_1 oxide.

utilized by him and his collaborators in the development of a very simple and satisfactory technic of vitamin K therapy.[21] The same investigators, in unpublished work which they have kindly permitted me to mention, have found that vitamin K_1 oxide likewise forms very stable emulsions. Initially, the emulsions were prepared by dispersing 10 mg. of the oily vitamin or oxide in 1 liter of 10 per cent glucose solution, but in the more recent work it has been found that the large volume of water is not necessary. A dispersion of 10 mg. of vitamin K_1 oxide in 15 c.c. of solution has been employed clinically with distinct success; for example, the intravenous injection of this emulsion promptly reduced the prothrombin clotting time of a patient from 90 to 19 seconds. The emulsions are prepared by the very simple expedient of mixing an alcoholic solution of vitamin K_1 or its oxide with a suitable volume of glucose or saline solution and shaking the mixture for a minute or two. The dispersion mentioned above was prepared from a solution of 10 mg. of the oxide in 3 c.c. of alcohol and 12 c.c. of glucose solution, but the proportions can be varied over a considerable range. Thus the volume of

glucose solution can be decreased to 7 c.c. satisfactorily. Emulsions containing as much as 10 mg. of the oxide in 10 c.c. of solution are smooth, bluish white suspensions containing no visible oily droplets, and those that I have prepared have shown no sign of separation over a period of five months. The suspensions can be autoclaved, and may prove to remain in a dispersed condition for prolonged periods. Dr. Seligman suggests that perhaps the most convenient procedure is to autoclave a suitable volume of the alcoholic solution of the oxide and, when an emulsion is required, to draw this into sterile glucose or saline solution in a syringe and shake the mixture prior to injection.

With the introduction of vitamin K_1 oxide and the development of this simple technic of preparing emulsions, it appears that the physician has at his disposal a practically ideal agent for vitamin K therapy.

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THE STATE OF SENSORY AND MOTOR CENTERS IN PATIENTS WITH HYPOTHYROIDISM *

By Norbert Enzer, M.D., F.A.C.P., Ernst Simonson, M.D., and Samuel S. Blankstein, M.D., *Milwaukee, Wisconsin*

Introduction

Increased fatigability and sluggishness are notable complaints and symptoms of patients with endocrine disturbances, particularly in those with a reduced metabolic rate. Since increased fatigability results also from mental work and is present even under resting conditions in these patients it occurred to us that it might be due to an impairment of some functions of the central nervous system. The metabolism of nerve tissue, like that of other tissues, is influenced and regulated by hormonal factors, particularly when oxygen utilization is affected. Disturbances of nervous functions are, therefore, to be expected when there are pathological alterations in the endocrine system. It appears probable that nerve cells cannot maintain their normal excitability if their metabolism is diminished or altered. It seems important to know if fundamental functions of the central nervous system are impaired in patients with endocrine disturbances.

For this investigation we chose simple methods, applicable in clinical laboratories. As an example of a sensory function we chose the flicker phenomenon. The fusion frequency of flicker is that rate of successive light stimuli at which the sensation of flickering disappears and becomes the same as continuous illumination. The fusion frequency of flicker depends on chronaxie, latent period and refractory period of the retina, the nervous pathways, and the visual centers. Since in any measurement of sensory functions it is difficult to differentiate between sensory receptor organ and center, it is probably more appropriate to speak of the retino-cortical system.

The retina, however, is regarded by many authors (for bibliography see Granit [1]) as a projected part of the central nervous system, and Elsberg and Spotnitz [2] recently showed similarities in fundamental retinal responses to general laws of excitation and inhibition established by Sherrington on the flexor reflex. Therefore, it may be assumed that such general disturbances as decreased metabolism would affect visual centers as well as the retina. In any case, the fusion frequency of flicker is regarded as a fundamental visual function (Hecht,[3] Crozier [4]). We found that the fusion frequency of flicker is decreased in fatigue of the central nervous system produced by occupational work (such as typing, secretarial work, laboratory work, etc.[5]). A decrease of fusion frequency in patients in the resting condition, therefore, would explain a decreased resistance against fatigue.

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The motor function may be subdivided into absolute muscular force (strength), endurance, speed and skill (McCurdy [6]). These functions concern different processes; they may be increased by training independently of one another. As sluggishness is the prevailing symptom of many patients with decreased metabolic rate, the measurement of maximum speed of movements would seem to be important and informative.

It is known that many motor impulses are necessary for the accomplishment of one voluntary movement. The smaller the leg and the less the inertia, the greater is the possible maximum frequency of movements, and the closer this maximum would be to the actual frequency of motor discharges in the centers. Lehmann [7] has shown that there is a close relationship between the frequency of finger movements and the frequency of impulses in the motor centers, so that it is possible to calculate the motor frequency of the centers from an analysis of finger movements. In fatigue of normal subjects, the time of discharge is lengthened and thus the frequency is diminished.

For these reasons the measurement of the maximum speed of finger movements was chosen for study of the state of motor centers. The frequency of finger movements can be related only to the function of the motor centers, because no other peripheral physiological function is involved demanding any considerable increase of respiration, circulation or metabolism. In connection with this it may be mentioned also that the fatigue in working with the finger-ergograph is due to fatigue of the motor or sensory centers as shown by Mosso, who produced muscular contractions by electrical stimulation applied immediately after complete voluntary fatigue. The maximum speed of finger movements as well as its drop was measured during a one minute performance.

Thirteen patients with decreased metabolic rate and with a diagnosis of primary or secondary hypothyroidism were studied. Among them were two patients with outright myxedema and one patient with symptoms of myxedema. All of them were treated with thyroid preparations. In table 1 the minimum value of the metabolic rate is indicated as well as the last value taken a few days before our experiments. Most of the patients (cases 1, 3, 4, 5, 6, 7, 9, 11) were overweight or had a tendency to gain weight. The most uniform feature of this group of patients was the increased blood cholesterol content (between 202.4 and 490.0 mg. per cent). The cholesterol content was not determined in case 3 (myxedema); cases 4 and 1 were included although their metabolic rate was normal, because both were obese women with premature (4) or artificial (1) menopause. The normal range of the basal metabolic rate is rather wide; therefore, a normal value does not necessarily exclude some hypofunction of the thyroid gland.

TABLE I

Fusion Frequency and Motor Frequency in Patients with Hypothyroidism

Pat. no.	Sex	Age	Diagnosis	Decrease of BMR in % of normal stand.		Tendency to overweight	Bl. cholesterol in mg. %	Fusion frequency flashes per sec.	Max. motor frequency impulses per 10 sec.	No. of decreased max. or min. values of motor frequency out of a total no. of 8 values
				Min.	Last month					
1	F	43	Artificial menopause	−5.0	−5.0	+	282.5	37.6; 35.8 36.8	45; 43	7
2	F	37	Myxedema	−22.2	−11.7	−	490.0	32.8	47	8
3	M	36	Myxedema	−39.4	−39.4	+	——	35.4; 35.0	34.0	8
4	F	33	Menstr. ceased, gained 90 lbs. during last wks.	——	+6.5	+	223.0	37.6	70	1
5	F	15	Hypothyroid symptoms of myxedema	−25.0	−25.0	+	250.0	33.6	34	2
6	F	54	Hypothyroid; hypertension bl. pressure 190/110	−10.6	−8.0	+	232.6	33.6	72	3
7	F	39	Hypothyroid	−10.5	−9.3	+	234.7	40.8; 40.8	43	3
8	F	34	Hypothyroid	−24.9	−21.3	−	228.4	38.4	65	—
9	F	50	Hypothyroid	−21.7	−21.7	+	282.5	40.0	65	—
10	M	47	Hypothyroid	−20.5	−20.5	−	224.1	35.2; 34.8	57	1
11	F	46	Hypothyroid	−12.2	−10.3	+	394.1	34.8; 34.4	53; 53	6
12	F	56	Hypothyroid; hypertension bl. pressure 170/110	−22.8	−22.8	−	409.8	33.2; 36.0*	46; 51*	6; 5*
13	F	50	Hypothyroid	−29.1	−29.1	−	202.4	36.6	60	2

* Condition improved.

Methods

We used a known rotator arrangement where the beam of light from an electric bulb (25 watt Mazda) was interrupted by a rotating disk with four identical openings. The subject was seated with his head placed on a chin rest so that the distance from the illuminated area to the eye was kept constant at one meter. The speed of the motor was increased until fusion occurred. The number of rotations was measured by a revolution counter and a stop watch. The subjects were examined under the following standard conditions: the vertical intensity of illumination of the surrounding field at the plane of the illuminated area was two foot-candles; the size of the illuminated area was 100 sq. mm., equivalent to a visual angle of ½ degree. The relation of the four openings (flashes) of the rotating disk to the dark intervals was 64: 36, i.e. 64 per cent of the whole cycle. The intensity of illumination of the test patch was 0.0039 candle power per sq. cm. Binocular central vision was used. Our results concern the fovea exclusively. The time of exposure was 1.5 sec. The accuracy with which the values can be reproduced is high; the variation of the values, taken in the same experiment does not exceed 1 or 2 cycles per sec. The daily variations do not exceed, as a rule, 3 to 4 cycles, provided that the subject's condition is the same.

For the maximum frequency of finger-movements the following method was used: the patient stood in front of a Cenco Impulse Counter, placed on a table. He was asked to press the button with his middle finger as fast as he could do it, until the stop signal was given, after one minute performance. After one minute pause, the test was repeated. First the right hand was examined and then the left hand in the same way. During the performance the number of contacts per each 10 seconds was counted by means of a stop watch. Thus the frequency is given in number of impulses per 10 seconds. The frequency drops during the performance from an initial high value (maximum) in a more or less irregular way so that the minimum value may occur as well in the last 10 seconds, as in the 30–40th, or 40–50th second.

The individual performance is characterized by the initial value (maximum) and by the minimum to which it drops independently of where it occurs during the performance. The difference between maximum and minimum values obviously is due to the fatigue of the motor centers during the performance. As the test is performed twice for each hand, we obtain 4 maximum and 4 minimum values as criteria of the performance.

In experiments on 45 normal subjects the daily variations were almost negligible; for instance for the initial (maximum) value of the right hand in the first performance they did not exceed 2 impulses per 10 seconds.

Results

Table 1 shows the values of fusion frequency (column 9). The three values in case 1, and the two values in cases 3, 7, 10, 11, and 12 concern

different examinations on different days. The fusion frequency of these patients is as remarkably constant as we have found in normal subjects. The higher value of the second examination in case 12 coincides with an improved condition of this patient. The lowest value of 45 normal subjects was 40.0 flashes per second, the normal average was 45.0. All values of the patients are below the normal mean value 45.0. The values of cases 7 and 8 are identical with the lowest normal value. It is probable that they are decreased. The values of the other 12 patients are lower than the lowest normal value; in these cases there is a definite pathological decrease. The decrease of fusion frequency is most pronounced in the cases with myxedema, 2, 3 and 5. In cases 6 and 12 the very low value may be due in part to hypertension. We have found in another series of experiments that the fusion frequency is diminished in patients with hypertension. The mean value of the whole group is 36.3, compared with the normal mean value of 45.0. The vision of our patients was normal or corrected to normal. The results show a definite decrease of fusion frequency in these patients.

Table 1, column 10, shows the values of the maximum (initial) frequency of finger movements per 10 sec. for the first performance with the right hand. The lowest normal value of a group of 45 subjects was 59, the mean value was 69.7 impulses per 10 sec.

Two patients (cases 4 and 6) showed values higher than the normal average; and in eight patients the values were lower than the lowest normal value. The average of all patients was 56.8, compared with the normal average of 69.7. The difference between the normal subjects and the group of patients is still more manifest, if all eight maximum and minimum values are considered. Column 11 shows the number of pathologically decreased maximum or minimum values, i.e. of values lower than the lowest corresponding normal value. With the exception of only two cases (cases 8 and 9) at least one of the values is lower than the corresponding lowest normal value. In the myxedema patients, cases 2 and 3, all eight values were pathologically decreased. Case 3 was not able to carry through the performance, therefore the exact minimum could not be determined, but there is no doubt that all eight values were considerably lower than the lowest normal values.

The drop of motor frequency during the performance indicates the fatigability of motor centers. We found in our 45 normal subjects that the drop of frequency depends on the initial frequency in a straight-lined function; the higher the initial frequency the greater is the drop during the performance. Figure 1 shows this relationship for the first performance of the right hand (ordinata = drop of frequency, abscissa = initial frequency). The values of all patients lie above the full line, with the exception only of case 10; that means that the drop of frequency is greater than in the normal subjects. The fatigability of motor centers in our patients is increased and it is interesting that this weakness of motor centers is very pronounced in cases 4, 6, 7, and 8 who showed a normal initial frequency.

There is no correlation between the decrease of fusion frequency or the frequency of motor impulses and the diminution of basal metabolic rate or cholesterol content of the blood. There is no relationship between the decrease of fusion frequency of flicker and the frequency of motor impulses, although both functions are diminished.

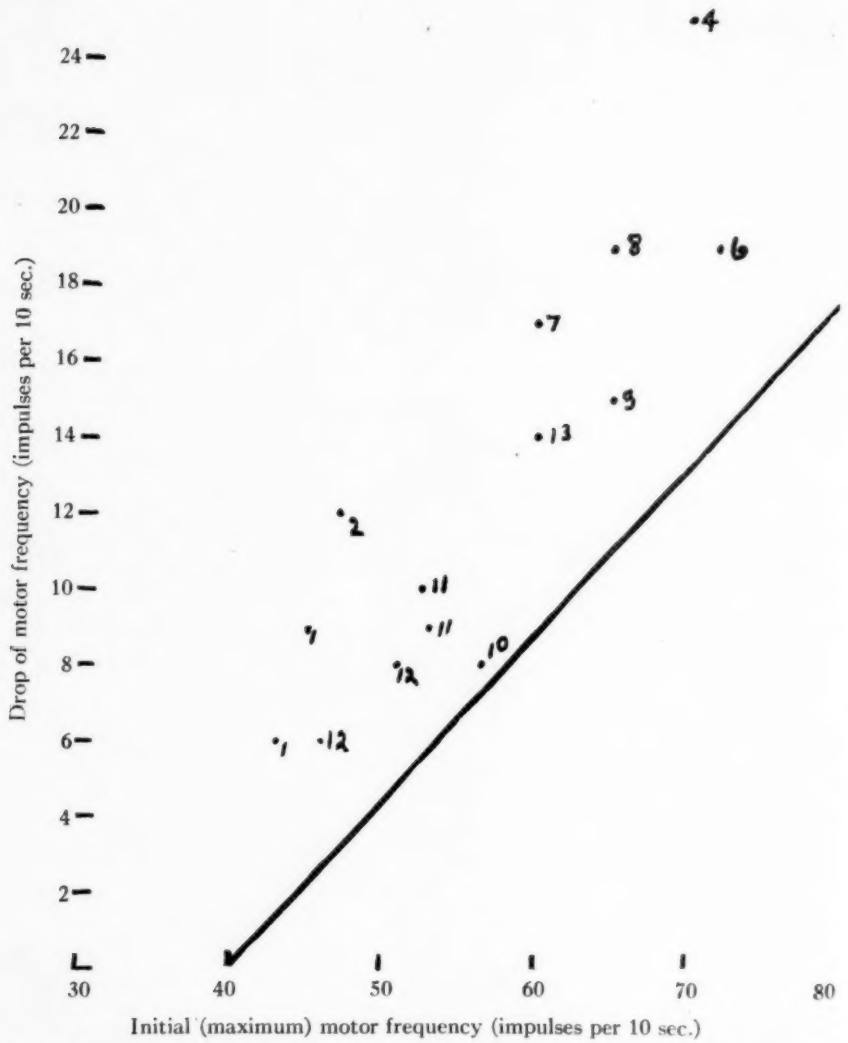

FIG. 1. Drop of motor frequency during the performance (right hand) dependent on the initial value in normal subjects (drawn in full line: average of 45 subjects) and of patients with hypothyroidism.

The studies of Bertrand et al.[8] on the electroencephalogram in seven patients with myxedema corroborate our findings. These authors found a diminution of the amplitude, slow large waves with a frequency of 3 to 4

per second, absence of the Berger-rhythm and, what is especially interesting with regard to our results, absence of the reaction to visual stimuli. As in our experiments, there was no direct relationship between these changes of the electroencephalogram and the diminution of the basal metabolic rate.

Conclusions and Summary

The experiments show that the state of sensory (determined by the fusion frequency of flicker) as well as that of motor centers (determined by the maximum frequency of finger movements) is deteriorated in patients with disturbances of the endocrine system characterized by diminished metabolic rate and increased blood cholesterol content. In some patients the decrease of fusion frequency, in other patients the decrease of motor frequency is more pronounced. Eleven of 13 patients have values of fusion frequency lower than the lowest value of 45 normal subjects, the other two have values that coincide with the lowest normal values. These results explain the disposition to increased fatigability of those patients, as the fusion frequency of flicker is diminished in nervous fatigue. The weakness of motor centers is shown by the increase of the drop of frequency during the performance.

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THE CONCEPT OF PSYCHOSOMATIC RHEUMATISM *

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The results of psychological, particularly medical psychological investigation, pass through three stages of opposition, like a bill in Parliament. At the first reading they are said to be absolutely untrue; at the second reading, they are said to be abnormal and improper; at the third reading they are said to be trivialities well-known to everybody since the Flood.—DR. MAJOR GREENWOOD.

How do we differentiate between " true fibrositis " and " psychoneurotic rheumatism "? Before attempting to answer this question it is wise to consider the meaning usually attached to each of these terms.

DEFINITIONS

Fibrositis. This word stands for the idea that subjective complaints of localized pain and stiffness can commonly be related to localized objective findings such as nodules, thickenings and indurations which result from inflammation of fibrous tissue and fascia. The objective existence of these nodules, etc., can be demonstrated by palpation, and also by pathological examination. The etiology is obscure, but many consider that these abnormal formations are dependent on focal infections. Others, however, have maintained that they are secondary to metabolic upsets, whether dietetic or endocrine. Massage, especially if deep and if it hurts the patient, will in course of time rub away or liquidate these nodules, and with this there is disappearance of the symptoms. This is a pleasantly simple theory, but there are certain objections to it. For example:

1. Enthusiasts for fibrositis have claimed that they are able to palpate nodules in a very large percentage of patients who are in common language said to be suffering from " rheumatism " (non-arthritic), both by the laity and by the medical profession. To such enthusiasts, the problem of non-arthritic rheumatism is already solved. Unfortunately, many physicians, even after most careful examination are able to detect nodules only in a very small proportion of such sufferers. Extremists have, however, recently asserted that this is because sufficient patience and practice have not been given to the examination.
2. Nodules are frequently found in patients who make no complaint of rheumatism whatever.
3. The findings of certain early authorities on the pathology of these nodules have not been generally confirmed.

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4. Increasing doubt has been expressed about deep, painful massage being able to rub away fibrous tissue. (On general grounds we might expect this violent trauma to increase the fibrous tissue.)

5. The etiology is purely speculative.

In short, the commonly accepted theory of fibrositis is a top-heavy superstructure erected on some very simple clinical observations, namely that in certain patients with non-arthritic "rheumatism," thickenings and nodules can be felt on palpation in or near the region complained of, and these may be very tender to touch and pressure; also, in certain instances, sections of tissue taken from the nodule or thickening show minor pathological changes of an indeterminate and non-consistent nature.

Psychoneurotic Rheumatism. This ungainly term stands for the idea that upsets in the emotions may bring about upsets in the body including subjective symptoms of pain, stiffness and limitation of movement which appear on medical certificates under such names as muscular rheumatism, fibrositis, sciatica, neuritis, lumbago, pleurodynia, etc. It is recognized that the inclusive term of "non-arthritic rheumatism," as well as its localizing names, covers a hodge podge of illnesses entirely diverse in etiology and nature, but it is considered that a considerable proportion—perhaps 40–60 per cent of patients who have been for two months or more on the sick list—can be understood only in terms of a psychoneurotic concept. That pain may be a symptom of hysteria has long been accepted, but due attention has not been given to the aches, pains and stiffness which may accompany chronic psychoneurotic anxiety states or psychotic depressions. Moreover, recent evidence suggests that, in certain persons, upsets in the emotions may also bring about upsets in the physical body or soma; i.e., disturbance of the psyche (in the sense of the emotional self) antecedes and determines the nature of the disturbance in the neuro-endocrine system, which in turn brings about derangement in metabolism both general and local, leading to the formation of what many writers call "fibrositis."

In order to appreciate this point in practice, it is, however, necessary to supplement our routine physical examination with a psychological approach.

Medical Examination and Its Modern Supplement

Although the relevance of psychological factors to illness was recognized by physicians from earliest times, their importance and significance were forgotten during the nineteenth century as the mechanistic outlook began to dominate medicine. The modern study of psychoneurotic illness has enabled these reactions to be formulated in a scientific way, and there is now evidence available which demonstrates that any system of medical thought which neglects environment in its psychological aspects is misleading in its theory and often unnecessarily futile in its practice.

The basic medical examination of the teaching schools consists of instruction in (*a*) history-taking confined to an account of the procession in

time of somatic symptoms; (*b*) identification (diagnosis) of the faulty part or parts; (*c*) etiological investigation confined to those factors (physical, chemical or micro-organic) which an individual encounters with his *soma*. The range of observations elicited by this investigation, however, may be too narrow, and modern medical knowledge requires us to make a supplementary examination which includes:

(*a*) "Looking upon the man," i.e., consideration of the patient's face and manner.

Some doctors seem very insensitive to this aspect of a patient. Facial expressions which give us a hint that the illness may have emerged from emotional reaction may be divided into two extreme groups—the anxious, and the detached. The anxious face may be described as strained, tired, worried or hunted; it is associated often with fine tremors of the outstretched fingers—which are detected readily against a background of newspaper print; with tachycardia or visceroptosis. At the other extreme, the detached face may be restful, placid, complacent, smiling, or "spiritual"—in short, pathologically free from anxiety. It is associated sometimes with marked thudding of the aorta in the epigastrium. Detachment of face and manner is sometimes called "la belle indifférence" and usually indicates that the disturbing emotions, and sometimes also the situation which provoked them, have become dissociated from the consciousness of the patient.

(*b*) An etiological investigation which includes those factors which the individual encounters through his psycho-neuro-endocrine system, e.g., personal relationships, quarrels and bereavement, occupational problems, financial circumstances, and fears and knowledge of disease.

(*c*) Extension of the history-taking backwards in time, to include the disturbances in the psyche which preceded the disturbances in the soma.

The patient who develops physical symptoms during the course of emotional reaction tends to date the onset of his illness to the time when the physical symptoms first appeared. His preceding disturbances may have been very definite and very severe and included depression, lack of interest, inability to concentrate, feelings of futility and unreality, etc., but an account of these is not usually volunteered spontaneously. The patient's consciousness is dominated by his bodily symptoms, and those preceding disturbances are suppressed. We must, therefore, direct our investigation to two points in time, not only to the date of onset of the bodily disturbance but also to the date of onset of the various psychological symptoms which preceded them and may still accompany them. Sometimes we find that there is a lightening or release of the psychological symptoms when the bodily symptoms appear. Psychologists describe this phenomenon by saying that the emotion has become *converted* into the bodily symptoms. When the conversion is complete, the patient's interest is concentrated almost entirely on his bodily symptoms, the treatment he has received, the number of doctors he has visited, and the possibilities of securing further varieties of treatment. It is not always easy to induce such a patient to talk about the difficulties which he has met in life, because he repeatedly short-circuits the conversation back to his symptom, the treatments he has received, etc.

If we omit this supplementary examination, the true nature of many disorders including non-arthritic "rheumatism" cannot be established, and, as a result, treatment may be inappropriate. Recent researches and observa-

tions in psychosomatic medicine show very clearly the need for extending the scope of academic medical examination if action, i.e., treatment or prevention, is to correspond with reality.

The Contribution of a Psychological Approach to Etiology

A. The Etiology of Onset

When applying a simple psychological approach as a supplement to ordinary examination it is useful to arrange the findings as answers to these three questions of etiology of onset, viz.: (1) What kind of person was this before he developed pain, stiffness and limitation of movement? (2) Why did he develop these symptoms when he did, i.e., to what external events were they the response? (3) Why did he take these symptoms in the way he did? When we adopt this formula as a framework in which to arrange our observations, we often obtain answers such as the following:

1. *Kind of Person.* Many of the patients who develop non-arthritic rheumatism have fairly well defined psychological characteristics, e.g., they are unduly independent, excessively upright, have a high sense of duty, and are conscientious workers. In their own words, "They keep themselves to themselves." A psychiatrist would doubtless summarize these characteristics by the term "obsessional." Such patients are rigid, stiff or touchy people before they become ill, with the rigidity, stiffness and wincing responses of rheumatism, which from this point of view may be regarded as a manifest expression of their latent attitudes to life.

The previous medical history of patients with non-articular rheumatism also deserves a short comment. Many of them have on previous occasions suffered from psychoneurotic illnesses in the form of "breakdowns" or from psychosomatic illnesses—not only the ill-defined gastritides, but also the radiologically confirmed peptic ulcer, or the irrefutably recurring bronchitis. It is usual for nervous breakdowns, gastritis and peptic ulcers to occur earlier in the time sequence than rheumatism and bronchitis. The triad of peptic ulcer, rheumatism and bronchitis is one which crops up again and again in the medical history of middle aged "chronics."

2. *External Events.* As the kind of person who develops these symptoms tends so often to keep himself to himself it is not always easy, especially in a single interview, to elicit the environmental factors or external events which precipitated deep-seated emotional reaction. However, after ordinary examination has been made it is useful and often helpful to sit back and slowly say: "It sometimes happens that symptoms such as yours (and here the examiner details them), begin at a time when a person is under some mental stress, or distress, or strain, or upset, or indecision. (Then after a pause) Does this happen to apply to you?" The question should not be pressed, but often the patient immediately and spontaneously tells the Doctor his difficulties, or he may do so at a second interview after a period of rumina-

tion. By means of this question, addressed meditatively to the mid-air, so to speak, it is often possible to discover from a patient how shortly before the onset of his rheumatism he met with some very disturbing event, e.g., the loss of a beloved person, of money, of career, or difficulties in his occupation. Thereafter the following sequence of happenings may be traced. The frustrating events provoke emotional reactions, especially those of grief and rage as well as of guilt, and these are associated with feelings of soreness and hurt. This inward (or mental) pain and anguish is in turn displaced into outward (or physical) pain and anguish. The latter, indeed, is often the measure of the intensity of the former. With the emergence of the bodily suffering there is usually some lightening of the mental suffering, and the attention of the patient becomes focused on his rheumatism and thus released from his life's problems and inner tensions.

3. *The Manner of the "Rheumatism."* Having noted how physical pain may be the expression of mental pain, and how physical stiffness and limitation of movement may be the outward and visible signs of a corresponding attitude to life, we are now faced with the following question. Why do particular persons select particular sites of the body for these "rheumatic" manifestations? (I have discussed this problem fairly fully elsewhere.) It may be said here that, in addition to considering previous injury or disease which may render a site "inferior," account must also be taken of the symbolism of the symptoms. For example, pain and stiffness in the posterior midline, either at the back of the neck, between the scapulae or in the lumbar regions, often symbolize inward feeling of resistance, obstinacy and resentment. Again, pains in the arms and legs associated with numbness, tingling, deadness and losses of power, may symbolize repressed desires to attack (aggression). Thus it is sometimes useful to ask certain patients with "sciatica"—"Whom or what do you want to kick?" Nor must we forget the symbolism of the left side, which in the human psyche is the side of the body related to sinister feelings of loss, evil or magic. Only when we begin to take note of whether a unilateral pain is on the left side or the right do we begin to learn how dominant are left-sided symptoms in non-arthritic rheumatism. In this connection mention may be made of the typical (but seldom realized for what it is) "left shoulder neuritis" which so often is a *neuritis of deprivation,* not, however, of vitamins, but of a married partner or other dearly beloved person or object. It is common in widows and widowers, and in married persons who are estranged or separated, whether through disagreement, by long illness, or by distance of land and sea. But if these matters are not sought out they will not be volunteered.

B. The Etiology of Recovery

When we have discovered the relevance of the psychological approach to the etiology of onset, we can then begin to take note of its value as an aid to understanding the etiology of natural recovery, i.e., why do patients,

even in the absence of treatment, begin to get better when they do? When we inquire into such recoveries after a long period of incapacity, we find that many of these patients have encountered some new environmental factors which lessened the adverse pressure of circumstance, made life bearable again, and brought about a slackening of resentment. The process indeed may be likened to that of the child who won't play, who decides to join in the game again.

C. The Etiology of Prevalence

The psychological approach may also provide a contribution towards our understanding of the geographical distribution of non-arthritic rheumatism which, it is now accepted, cannot be related to climatic influences alone. For example, it is established that non-arthritic rheumatism is unusually prevalent in the northeastern districts of Scotland round Aberdeen. This area may be regarded as fairly cold, but not unduly wet. It has, however, other features which may also be highly relevant. Its inhabitants are classical examples, whether by inheritance or Calvinistic culture, of the "obsessional" type already described which (as investigation of individual patients suggests) is especially liable to develop non-arthritic "rheumatism."

The prevalence of rheumatism over a period of years may also be related to the increase or diminution of what may be called the pressure of noxious psychological communal environment. For example, in Scotland during recent years, at a time when unemployment was increasing and people were losing the vision of life, incapacitating sickness rose very considerably, especially in the chronic groups. The interesting feature of this rise was that it was made up entirely of those diseases which are now being recognized as psychoneurotic or psychosomatic. Leaders in the rise were peptic ulcer, gastritis, nervous debility, pleurodynia and rheumatism (Halliday, 1938).

It must be admitted that medical men who are unaccustomed to applying a psychological approach to their "cases of fibrositis" will assuredly consider this newer (and older) way of looking at things as very curious and quaint, having nothing to do with the case. Unfortunately, so often it has practically everything to do with the case. If any such can overcome their resistance, cease "thinking" (in the Hunterian sense) and condescend to "try" (i.e., supplement the usual physical examination by inquiries along the lines indicated above), they will find how often this method of medical examination not only "fits" but also "works."

Psychoneurotic Rheumatism in Practice

In practice psychoneurotic rheumatism takes many forms, but I have found the following a useful classification.

1. *Hysterical Pains.* Among the insured patients whom I see in my capacity of medical referee, such pains are comparatively rare, except in persons engaged in occupations which expose the individual to excessive bodily danger. This applies particularly to workers at depths (typically:

underground miners), and workers at heights (typically: steel erectors, slaters, window cleaners and steeplejacks). Other common occupations dangerous in this respect are those concerned with the manufacture of explosives, as well as those sports and pastimes, e.g., football, which involve a high degree of bodily risk. There is known to be a close relationship between hysteria and threats to bodily preservation. This has recently been emphasized by Kretschmer who notes how often hysteria " develops out of a gradually progressive anxiety for one's safety." Unfortunately, many persons with " hysteria simulating rheumatism " are admitted all too readily to centers for physiotherapy, with consequent fixation of the symptoms. There are many reasons for this, e.g., (*a*) the still lingering superstition that hysteria is rare in men; (*b*) the failure to take note if the person's occupation is a dangerous one; (*c*) the omission to examine for marked thumping of the aorta in the epigastrium—a sign not necessarily diagnostic, but suggestive when present.

2. *Pains, Aches, Stiffness and Limitation of Movement as Episodes in Chronic Psychoneurotic Anxiety States and in Psychotic Depressions.* These are very common. In my experience as a medical referee of the insured persons, about one-third of these patients who are labelled by their doctors with terms indicative of non-arthritic rheumatism, and who have been on the sick list for several months, readily fall into this category. A full account of this inquiry is given elsewhere (1937). The reason for the non-recognition of the true nature of these disorders is the failure of academic medicine to indicate the need for a simple psychological approach as a supplement to ordinary physical examination. In the absence of observations made by this technic of approach much incapacity preventable at the beginning becomes permanent and fixed.

3. *Fibrositis.* This note unfortunately must be confined to a personal confession. I happen to be one of those who often fail to discover by palpation fibrositic nodules vouched for by other medical men, although I must admit that sometimes, in the presence of an enthusiastic demonstrator, I am led to " imagine " I can feel them. This does not mean that I am unacquainted with nodules. I discover them from time to time, but, again, unfortunately, I seem to find them as frequently in persons who have no complaint of rheumatism as in those who have. Because of this personal inability, I have hesitated to make a serial inquiry about the prevalence of fibrositis in any group of persons labelled " non-arthritic rheumatism " by their medical practitioners. The term fibrositis, in virtue of its implied idea of inflammation, has always seemed to me a misleading one in clinical medicine, although of value to a pathologist. Fibrositis in the sense of inflammation of fibrous tissue (as, for instance, after sore throat) is understandable and in such instances my dominant clinical impression is that the patient is physically ill. But in the so-called " true rheumatic fibrositis " I am impressed far more by the patient's behavior and attitude, inasmuch as it conveys the feeling that I am confronting a strained, unhappy distraught

individual and that the fibrositis is a purely local manifestation in a process of reaction of the person as a whole. This clinical intuition is difficult to put over in words, but the phrase " looking upon the man " seems to summarize it in a communicable form. In other words, to be misled by " itis " in the word fibrositis and to concentrate on the local phenomenon of nodule or induration tends to make us miss the value of the concept of psychosomatic disturbance, or, if we like to use the term " disease," of psycho-neuro-endocrine disease.

Four Cases of " Fibrositis "

I have selected four patients to illustrate in outline the practical issues raised in the paper.

Case Reports

Case 1. Following the publication of my preliminary report (1935) on psychological factors in relation to rheumatism, I received a letter from an elderly surgeon in which he told me that he had at last come to understand the true nature of the serious " rheumatism " from which he had suffered some years before. He gave me permission to quote " his case."

Until the age of 60 he " had never known what rheumatism was," but at this time he became ill with severe pain in the left shoulder, upper left arm and left costal areas. He attended various specialists, who agreed that " the case was one of severe and extensive fibrositis." He was persuaded to go to a Spa, but was so crippled he had to be lifted in and out of the bath. Various forms of physiotherapy were given with no improvement. Finally his counsellors decided that the only thing to do was to " break down " the fibrous adhesions under an anesthetic. The patient, however, refused this procedure and returned home. After a further month of agony " quite surprisingly I got better within a few days."

As regards the etiology of onset, particulars of the " kind of person " he was are scanty. He was attached to the staff hospital, and on reaching the age of 60, the usual retiring age, he expected to be retained " in view of his services." To his shock and surprise he was informed that he was to be retired. This hurt him very much—" I lived for my work." He had little to do, and fell into a state of boredom, depression and resentment. During this unhappy emotional phase his rheumatism emerged. As regards the etiology of recovery, about a month after his return from the Spa he received unexpectedly " an offer of an appointment as surgeon in a neighboring hospital. Life became worth living again. I got better within a few days."

Comment: This patient presents an example of left-sided symbolism, the sinister event being the loss of the loved object, in this case his work and reputation as a surgeon. Was he " a case " of fibrositis or of psycho-neuro-endocrine rheumatism? We may accept the presence of " true fibrositis " —leading authorities had confirmed it. However, it is evident that the psychoneurotic concept cannot be omitted in any understanding of the phenomena. A better all-in descriptive term would be psychosomatic non-arthritic rheumatism, or alternatively psycho-neuro-endocrine disorder with fibrositis as a dominant physical symptom.

This patient appended as a postscript to his letter the following: " I happened to read your articles on rheumatism when I was on vacation as a ship's surgeon. At

that time I had in the sick bay a fireman who had taken ill some days before with severe pain in the left neck and lumbar region which I ascribed to fibrositis. Armed with a new viewpoint I visited him and tried to persuade him to talk about the kind of thing you mentioned. Sure enough, I caught a fish! I found that at the last port of call he had been fined and logged for drunkenness and that the chief officer had told him that the Company would dispense with his services when he reached Liverpool. The man's previous record had been good, but he had evidently received a letter from his wife which worried him and had set him on a drunken bout. Anyhow, after his interview with the Chief Officer he became oppressed with a feeling of hopelessness and resentment. At times he said 'he did not know where he was,' and he pictured himself not being able to secure a job again. Some days later, the rheumatism appeared. I thought I would try an experiment in treatment in the light of this information, and I explained my idea to the chief officer who was interested and who agreed to inform the man that his sins were forgiven and his misdemeanor would be officially erased. Next day, the pains had almost cleared, and on the following he resumed his duty. It seemed to me that if I had not made the further inquiries which I did, the man would probably have been on the sick list until we reached Liverpool, and after that would probably have haunted the hospitals receiving many courses of massage."

Case 2. A medical practitioner told me the following: "I had a patient, a childless widow of 38 years, who after the death of her husband eight years previously developed a neuritis of the left arm which lasted for nearly two years. Rather than return to her family she decided to take an apartment house and to earn her own livelihood. She obtained a secretarial position in a warehouse, and remained cheerful at work and had a fairly extensive social life including attending church and bridge parties. Six months ago she consulted me because of severe pains in the lumbar region. I could make out nothing definite, but she seemed in considerable bodily distress. I tried to find out from her if she had any difficult emotional experiences in her life lately, but she denied this, and admitted only to some overwork at the office. I accordingly sent her to see a physician at one of the hospitals, and he diagnosed widespread fibrositis and recommended a course of physical treatment including massage. However, yesterday, to my complete astonishment (I should not have thought it of this woman) I learned from private sources that for several years she had been associating with a married man who was rather a bad lot. It appeared that shortly before she reported sick he had got into financial difficulties and had begun to blackmail the patient for money threatening her that if she did not give it to him he would inform her relatives that she was his mistress.

Comment: I have included this patient to illustrate the difficulty of discovering relevant etiological factors in persons who keep themselves to themselves. The "lumbago" symbolizes resentment, resistance, threats to pride and independence and other related ideas. The term "fibrositis," granted that nodules were present, again seems inadequate and even misleading.

Case 3. This was a married man of 38 years who in March reported to his Insurance Practitioner with a complaint of severe pain between the scapulae and of pain and stiffness in the left lumbar region. The patient explained to the doctor that on the previous day he had been thoroughly soaked and together they accepted the etiology of the "rheumatism" to be a "chill." The doctor diagnosed fibrositis, prescribed aspirins and some liniment. The patient was still on the sick list when I saw him in June, three months later. He looked tired and anxious and was inclined to be resentful because he had been summoned before a medical referee. I was not able to

satisfy myself about the presence of nodules. I then investigated the details of his soaking and elicited the following:

He was a hard-working conscientious man anxious to do the best for his four children. Eight years previously he had had a perforating gastric ulcer, but since that time he had been well, apart from a severe and prolonged attack of bronchitis two years previously. He had had no previous rheumatism apart from occasional "twinges." As regards employment, apart from his two periods on the sick list he had been continuously at work, but in January, through no fault of his own, he had fallen out of employment. With this he became very depressed and for the first time his thoughts turned to the political system which allowed such things to happen to respectable, decent working men. During this mood of depression he was told by the Labor Employment Bureau that if he visited a firm in a town eight miles distant, he would probably secure a job. He was by now in debt, and he had no money to pay his bus fares. Accordingly, he decided to walk, but a lashing rainstorm came on, and as he plodded through it his temper rose. In his own words "he was so upset in his feelings that he decided to refuse the job even if it was a good one," and in actual fact this is what he did. He returned home in the pouring rain and when he got there, he refused to speak to his wife and lay down in his bed. When he tried to get up next morning he found he was unable to do so because of his pains.

As he related this story, he showed considerable emotion and shed some tears. I told him how often pain such as his came on during a time of deep-seated mental stress. He seemed to see the point, and admitted that such things were possible. We talked matters over, and although I retained him on the sick list, I received a letter from him the following week telling me that he had now secured some work and was "almost well."

Comment: This man may or may not have had fibrositis. He was certainly ill. Note the previous history of peptic ulcer and bronchitis. The soaking may have been a factor in the etiology of onset—it is not possible to say, but so often one finds that patients "rationalize" these physical encounters (example, chill, heat, cold, bad air, soaking, etc.), and further inquiries reveal that the dominating etiological factors were psychological.

Case 4. This was a married woman aged 30, a bus conductress, who on July 18 developed pain, stiffness and swelling of the left great toe so severe that she had to be carried from her work and put to bed. There she remained and about two weeks later she developed pains in the left shoulder and left neck as well as pains and swelling in the region of the left sternoclavicular joint. She remained in bed under the care of her insurance practitioner until September 20. Eight days later she was referred to the out-patient department of a hospital where, after roentgen-ray examination and elimination of gonorrhea, a diagnosis of periarthritis was made. She was given courses of massage, heat and electricity, and I did not see her until November 4, when my clinical notes read as follows: "Stiffness of both joints of left great toe but no definite swelling. Definite thickening—almost as if fluctuant—but no tenderness of left sternoclavicular joint; also slight thickenings over the joints of the second and third left sternocostal junctions." However, two other points impressed me. Firstly, her manner which was placid, smiling and composed. Secondly, it was extraordinary to find these physical signs confined entirely to the left side. Together these points suggested the possibility that psycho-neuro-endocrine mechanism must have played a prominent part in inducing her illness.

Her story was as follows. She was married in 1928, and a child was born in 1930. That year also her husband left for America. At first he was able to send her money

but this lasted only a short time. Rather than depend on her parents she decided to take up employment as a bus conductress. She was able to do this and live with her parents who looked after the child. Although her husband was unable to support her he continued to write regularly, but in January of the present year he ceased writing and as the months passed she thought he had deserted her. Also in January she was transferred to another town and had to live in lodgings. This not only reduced her income but also prevented her from seeing her child. She became depressed and sleepless. Her father was continually writing her to get into touch with the proper authorities with a view to tracing the whereabouts of her husband but she was afraid to do this in case her worst fears might be confirmed. On July 15 her landlady went on holiday and she transferred to new lodgings. She felt totally alone and abandoned and could see no way out for the future. Three days later she collapsed while on duty with severe pain in the left great toe.

It is noteworthy that she actually did hear from her husband on October 20 and he stated that he had at last secured a job and was looking forward to having her out beside him before long. According to her statement this letter made her feel better and since then her symptoms had improved somewhat. As the woman related her symptoms she broke down and after this we had a talk about the meaning of her illness and where the course of her life lay. She willingly accepted the sequence of events in relation to her symptoms. I asked her to come back three days later. She had lost that smiling detached facies and was somewhat anxious looking. Moreover, the swellings had entirely disappeared. Eighteen months later I learned from her doctor that following my two interviews she had resumed work and had never been on the sick list since.

Comment: The term periarthritis is totally inadequate as a summary of this patient's illness and as a guide to action. The psychological approach contributed definite findings regarding the etiology of onset in respect to (*a*) the kind of person, (*b*) the external events, (*c*) left-sided symptoms. (I must admit, however, that I have no idea why the great toe and sternoclavicular joints were chosen.) It also contributed towards an understanding of the etiology of recovery—the letter from her husband, the telling of her story, innocence replaced by insight, and the return of the will to work for her child. This problem, the etiology of recovery—why does a person get better when he does?—has been, in the past, far too much neglected.

These examples must not be regarded as isolated ones. Any medical man will find similar cases in his every day practice if he cares to look for them. Any specialist in rheumatism who neglects the concepts contained in the term " psychoneurotic rheumatism " may be compared to a motor mechanic who is content to repair a hole in the tire with the very newest of patches and solutions, but who considers it beneath his notice to search for the nail to which the lesion was secondary. And the nail, like the underlying psycho-neuro-endocrine disturbance, tends to bring about recurrences of " the condition " either at its original site or elsewhere.

Conclusion

How do we differentiate between " true fibrositis " and " psychoneurotic rheumatism "? At present the answer is, by working more and talking less. In other words, the differentiation depends on the nature of the observations

we make rather than on the views we hold. In practice this means the following:

1. Examine the patient honestly and do not detect abnormalities which are not there. If nodules and indurations are not present do not, on any "theory of fibrositis," deduce their presence. If nodules are demonstrable, remember that the etiology is not known in any scientific sense.

2. Whether nodules are present or not, always include a *psychological approach* as a supplement to routine medical examination. When they are absent, this approach may point the way to a diagnosis of hysteria, chronic anxiety state or psychotic depression. If nodules are present, a supplementary examination may indicate very clearly how the rheumatism emerged during a period of intense emotional stress, and, as we come to realize how often "fibrositis is cured" when emotional stress is relieved, any observations we may make on the life situation of the patient may provide us with guidance for action (treatment) much more valuable than routine courses of physiotherapy which take no cognizance of important etiological factors.

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SCHIZOPHRENIA; A NEUROBIOLOGIC APPROACH *

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THE approach to an understanding of the mechanisms responsible for mental illness has definitely entered a new phase, one characterized by attempted synthesis of data acquired through distinctly separate methods of investigation. This is basically a neurobiological methodology which utilizes data ascertained by the various individual methodologies which are applied to the study of the development, form, and function of the nervous system. This approach attempts to bring psychological studies with their multitudinous ramifications to a physiological level; i.e., it is an effort toward the interpretation of psychological data in the terms of neuronic development and function. It attempts, by outlawing the dichotomy of psyche and soma, to view psychology and the development and physiology of the nervous system as part and parcel of the same thing, the mind being defined as the objective and subjective expression of the biophysical function of the cellular units of the nervous system.

Such a methodology picks up the loose ends of phylogenetic, embryologic, anatomic, biophysical, biochemical, pathologic, clinical, and comparative and human psychological studies of the nervous system and ties them into a unitary methodology which represents not the partial perspective of separate methods of investigation, with their conclusions based on incomplete data, but a total perspective or comprehensive schema.

Even the most superficial use of this method of investigation makes apparent certain principles of nervous function which have been either overlooked or, if discovered, not utilized in the synthesis of data which have gone into the formulation of etiologic doctrines in the past. By bringing phylogenetic studies and studies of comparative behavior into the scheme of investigation we feel that we have been able to draw certain conclusions which may serve to re-orient the investigative approach to and the interpretation of the neurodynamics behind so-called functional mental illness.

Schizophrenia probably represents the major problem of psychiatry. This is not only because it is so economically and socially important, but because a clearer understanding of the mechanisms behind the schizophrenic process can unquestionably throw considerable light on other psychiatric problems and lead to more concrete knowledge of neuropathology. It is for this reason that we are attempting to present here a neurobiological or comprehensive interpretation of schizophrenia.

For the most part, the nervous system has been studied without consideration for its phylogenetic status. Likewise psychological studies, while frequently taking into consideration phylogenetic processes, have not been fully

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cognizant of the importance of determining man's phylogenetic status other than to place him at the top of the phylogenetic scale. This is too static an interpretation. Man can not be considered as phylogenetically mature, as we will see. This is a most important consideration in any study of the function of the nervous system. By considering man as a phylogenetically immature creature, a being in transition, the synthesis of investigative data is simplified, many of the apparent antinomies arising from separate investigative methodologies are solved, and a better perspective of neural mechanisms and the behavior that results is obtained.

Phylogenetic Background

All living organisms, from the simplest protozoa to the highest metazoa, expend their vital energies toward the attainment of two specific goals, i.e., self and species maintenance. These goals themselves are served by three universal biologic impulses—the urge to seek sustenance, the urge for protection from inimical environmental influences, and the urge to reproduce the species in kind. To these impulses we give the terms hunger, self-protectiveness, and love. Intangible as these things may seem, they are, nevertheless, as real as life itself, and even the most superficial survey of phylogenetic development forces us to accept, as a scientific fact, that these are the biologic constants which determine behavior throughout the phylogenetic scale from ameba to man.

In protozoa, protoplasmic irritability serves to adjust the organism to its environment and to adjust the internal economy of the organisms so that these ends are best served. In metazoa, because of cellular specialization for division of labor, the nervous system is developed for the specific purpose of maintaining the internal and external adjustment of the organism in its struggle for species and self-maintenance. Thus, it is at once apparent that, from the beginning, behavior and the structure and function of the nervous system are inseparable, the one the manifestation of the other. The definition of the word " mind " is then limited to the sum total of the function of the nervous system. It is also apparent that all organismal behavior, as well as the structure and function of the nervous system, is determined primarily by the two essential biologic goals of all living organisms in response to the impulses of hunger, self-protectiveness, and love, and that these premises must serve as the basis for all interpretations of behavior or nervous function.

Phylogenetic progress is an almost interminably slow series of events in which many factors operate continuously. In general it is characterized by an increased range of mobility associated with varying morphological adaptations to a successively more complicated environment to which the organism must react to secure, maintain, and reproduce life. With the evolution of a new species of life eventualities arise which require more complicated mechanisms and more complicated behavior patterns for existence. This

necessitates a concomitant increase in the functional and structural form of the nervous system. However, before satisfactory behavior patterns are well integrated and stabilized a long period of experimentation with the environment, as well as adjustment of the internal milieu of the organism to these experiments, is necessary. Species maturity is measured by the stability and consolidarity of the species-specific engrams and their universality among individual members of the species. In terms of neurophysiology this may be expressed as the functional solidarity of the neuronic chains.

Functionally and structurally the phylogenetic development of the nervous system follows a distinct pattern and results in a progressive encephalization of the centers of control. The "master" of the entire nervous system is always found to be in its most cephalad portion. Likewise, the newest phylogenetic acquisitions of the nervous system, and, therefore, the least stabilized and consolidated or integrated by species experience, lie cephalad. Furthermore, each older level of function (phylogenetically inherited) is represented in each successive cephalad level so that it may be subject to modifications of function according to the environmental exigencies of the new species. This is essential for maintaining the internal milieu of the organism in satisfactory adjustment to the environmental contingencies with which the organism is faced.*

This means that each new species must pass through a period of transition characterized by two contiguous processes. New engrams must be worked out by experimentation with the environment. At the same time the newer nervous centers must assume control and dominance of older phylogenetic engrams. During this period of transition, the organism's behavior reflects this struggle between these two forces for dominance of the organism's behavior, i.e., reflects the struggle between newly formed engrams which are in the process of integration and old well consolidated phylogenetically inherited engrams. We find then that behavior during this transition period is unstable and varying in its manifestations, that it is, in fact, a compromise between two neural mechanisms, one well consolidated, the other in the process of being consolidated. Species maturity is reached only when the newer engrams attain complete dominance of older neural mechanisms.

In succession the midbrain, the thalamus, the corpus striatum, and finally the neopallium are developed with each in turn acquiring the "greatest compass of the control of behavior." With the acquisition of a highly specialized premotor and parietal cortex we come to man in whom we find the highest representation of the phylogenetic development of the nervous system: a nervous system in which there are "vague memories . . . of those centuries when the world was in its childhood."

* This statement leads to the conclusion that in vertebrates there is no actual division of the nervous system into the cortico-spinal and autonomic systems, a fact that is well substantiated by recent researches. These two systems, heretofore regarded as separate, are interrelated at every level of impulse integration and can not be considered distinct in any real sense. Phylogenetic studies would point to no other conclusion, and it is interesting to note how many errors could be avoided in theorizing on human physiologic processes if phylogenetic studies were included in the formation of these theories.

Man's development is characterized by a gradual loss of effective defensive and offensive morphological mechanisms for combating inimical environmental influences and a concomitant gradual increase in inventiveness. In its broadest sense we speak of this latter as intelligence. In its strictest sense it is the ability to form concepts which adjust the organism satisfactorily to its environment. Structurally, this ability to form concepts has been shown to be associated with the development of the human premotor cortex, that part of the nervous system designed as the great association areas where through synaptic neuronic associations, by cellular polarization (Kappers), uniquely human behavior is initiated. Many recent experiments definitely place the seat of conceptual ideation in this region of the nervous system. Therefore, from what we know of phylogenetic development and comparative behavior studies, it is apparent that intelligence or, as we prefer, conceptual ideation is man's biologic mechanism for use in his struggle for species and self-maintenance in response to the urges of hunger, self-protectiveness, and love, i.e., the mechanism through which he adjusts himself to the environmental circumstances of his life.

We find, however, that in man's immediate phylogenetic predecessors the struggle for species and self-maintenance is essentially an individualistic struggle in which the weak and the unfit are rapidly eliminated. Individual strength is the ideal; weakness is synonymous with annihilation. Mutual assistance among members of a species in the struggle for existence is found on only the most primitive scales when observed at all. These forms of life, those that survive, are morphologically adapted for success in an individualistic struggle with their environment, and their behavior patterns or engrams are so designed. In man the situation is reversed, for man, even when endowed with a high degree of intelligence, is no match for the destructive forces of his environment as an individual. Gregariousness became mandatory for man as he lost his morphological defenses against natural enemies.

Gregariousness is man's primary species-specific behavior engram. If we study the history of the human race as far back as we can go with scientific theorizing we find that this was probably the first specifically human engram to be developed and is today the best integrated and consolidated of man's species-specific engrams. How well consolidated it is we will see later. All other strictly human behavior engrams and neural mechanisms have this as the pattern or ground-structure to which they must conform. Now, for this to be a biologically effective mechanism it must be supplemented by other behavior patterns which conform to its essential form. A communal type of existence, just as a multicellular type of existence, presupposes some agency which will maintain harmony of function. Out of this need developed moral obligation, the keystone, in a biological sense of effective communal life. The moral obligation of which we speak is not limited to the popular conception of the term "morals," but refers to that obligation each individual living in a communal state must assume toward

others for the welfare of the whole. To quote Bergson who summarizes this well: "It is society that draws up for the individual the programme of his daily routine. It is impossible to live a family life, follow a profession, attend to the thousand and one cares of the day, do one's shopping, go for a stroll, or even stay at home without obeying rules and submitting to obligations. Every instant we have to choose, and we naturally (*due to species-specific engrams—Author*) decide what is in keeping with the rule. We are hardly conscious of this; there is no effort. In the ordinary way we conform to our obligations rather than think of them. The members of a civic community hold together like the cells of an organism. Habit (*species-specific behavior engrams—Author*), served by intelligence and imagination, introduces among them a discipline resembling in the interdependence it establishes between individuals, the unity of an organism of anastomotic cells." And just as the nervous system is the cohesive factor in a group of anastomotic cells, moral obligation is the cohesive factor in communal existence. Moral obligation, in this sense, is the means through which a gregarious or communal type of existence is made possible, and thus is the means by which human life for the individual and the species is maintained. It is man's second species specific behavior engram.

It is now to be noted that these two behavior engrams or patterns have become "unconscious" functions, functions which have become so well integrated through species necessity and experience as to be considered "instinctive." If one considers species-specific instincts as unconscious reactions or drives found universally among members of a species, then we can consider gregariousness and moral obligation as man's species-specific instincts. Because they are species-specific and develop with the acquisition of a highly specialized premotor cortex their master neuronic mechanism must be represented in this area. But it is to be remembered that they are superimposed upon the individualistic instinct-engrams which man has inherited from his immediate phylogenetic predecessors. Thus, if the laws of phylogenetics hold for man, and there is no scientific reason to theorize to the contrary, then the species-specific instincts of man must eventually assume complete dominance of these phylogenetically older individualistic instincts and modify them to conform to the newer scheme of living if man is to be considered phylogenetically mature. In terms of neurophysiology, the neuronic chains for these instincts must completely regulate and modify older and lower neuronic chains. We can only conclude from phylogenetic studies that these instincts are manifestations of neuronic patterns which are as much predetermined for the individual as are the cellular patterns of the heart or liver, patterns which have been consolidated by (phylogenetic and species) experience.

It becomes apparent at once that this dominance has not been effected. Man's behavior over the period of its recorded history, and we may presume before this, reflects a struggle toward this dominance which has never been quite achieved. Man's behavior is characterized by an endless struggle

toward intellectually ideal behavior based upon the laws of moral obligation, but is marked by that ebb and flow characteristic of experiment, is unstable and unpredictable, is fluctuant in its manifestations, is a never ending response to new and varied concept formation, and when broken down in analysis consists of an eternal conflict, both for the individual and the race or any of its component subdivisions, between individualistic animal urges and the urges of moral obligation and the intellectual concepts built around the concept or species-specific instinct of moral obligation. In the individual we daily see in every phase of behavior that this conflict is manifest, and in general we may discern it by the conflict of political, religious, and social ideologies for a "place in the sun." Man's behavior reflects a period of phylogenetic transition; a period during which new phylogenetic neural acquisitions (in this instance the human premotor cortex) are adjusting a new species internally and externally to its environment in an attempt to insure most efficiently species and self-maintenance. It is a period during which we would expect behavior to be "experimental," and we find daily evidence that it is. In terms of neurophysiology we find that man's behavior reflects a struggle for dominance of the neural mechanisms of the premotor cortex in its formulative stage over older phylogenetic centers with engrams which are well consolidated and integrated. It is in popular terms a struggle between human intelligence and animal instinct for dominance of behavior.

Therefore, from phylogenetic studies of neural development and comparative behavior we conclude that man is a being in transition, that his behavior reflects a conflict with varying compromises between his species-specific instincts of gregariousness and moral obligation, and the concepts built around these instincts, and the individualistic instincts he has inherited phylogenetically; and that this behavior reflects a functional attempt of an unstable and immature premotor cortex to dominate a stable and mature older nervous system in the struggle for self and species maintenance in response to the primal urges of hunger, self-protectiveness, and love. That this is of major importance in the development of the schizophrenic reaction we will attempt to elucidate.

Developmental Background

The development of the individual human fetus from conception to birth is essentially a rapid recapitulation of the phylogenetic development of the species. In the fetal nervous system the phylogenetically well integrated reflex and instinctive levels are established early. As an example, we find that the neuronic chains over which nervous energy flows for maintenance of cardiac action are intact and functioning by the fourth month of fetal life. Development within the fetal nervous system proceeds in relationship to the phylogenetic age of the part and does not proceed at the same rate in all parts of the nervous system simultaneously. Although many of the lower levels are functionally integrated by the fourth or fifth month of fetal life,

in the frontal lobes of a six month fetus " lamination has not yet appeared and the cells are of a uniform undifferentiate type (neuroblasts). They are small round cells with a close and readily stainable reticulum, but quite devoid of processes, and they lie embedded in a matrix which, in hardened and stained sections, somewhat resembles the grain in marble. In the eighth month embryo the neuroblasts are somewhat larger, the reticulum is less close and has less affinity for stain, but there are as yet no definite processes. At this age signs of lamination are very clearly seen in the frontal region of the cortex. In the motor area of the cortex of the eighth month embryo medium size pyramidal and also Betz cells are readily recognizable." [1]

At birth the structural development of the nervous system is far from complete. The phylogenetically newest areas have not fully begun to take form, the cells of the frontal areas of the cortex being barely recognizable as nerve cells. At birth the infant human being is, in truth, a " little animal," an organism without a frontal cortex. Intelligence is only potential and neocortical association centers are not developed or integrated.

From birth to physiological maturity, which we estimate biologically as full physical and sexual maturation,* the development of the human organism has as its goal " the functional integrity and dominance of the cerebral cortex." [2] By two weeks progress is apparent, for the " cells of the frontal cortex have made a rapid advance in development and are recognizable as nerve cells. A cell body is present, although the protoplasm of this differs from that of a mature cell, being very vacuolate and liable to break away. A few years after birth these cells have assumed their mature character and are in possession of dendrites, axons, and gemmules." We find that the development of the premotor cortex and, thus, the development of intellectual capabilities (capacity for concept formation) is gradual and proceeds along a definite plan from the more simple faculties to the most complex. It also reflects the steps of development of the human race from its evolution to its present state. It is an hierarchy of neuronic associations within the general hierarchy of levels of the complete nervous system, and development proceeds from level to level in an orderly manner, just as it does in the nervous system as an organ. Bolton [3] substantiates this by showing that development of the cortex takes place from within outward and that at birth the outer stratum of the cortex is little more than half the depth of the stratum of the adult and exhibits an aggregation of embryonic cells.

With the establishment of the need for a communal type of existence with its manifold problems of organization and integration, the need for a highly intricate method of communication between individuals is recognizable. Speech developed in man's early period of evolution as a specifically

* That degree of maturity at which the individual is physically equipped for his struggle for species and self-maintenance in response to the urges of hunger, self-protectiveness, and love, i.e., that degree of maturity which enables him to take his place as a mature member of society.

human mechanism and as a cortical function. Therefore, the development of the power of speech is in the infant the first objective manifestation of the functional integration of neuronic associations in the strictly human cortex.

The onset of speech is at about 19 months in boys and 18 months in girls. Karlin [4] reports on the neurodynamics of the development of speech and is quoted here to illustrate graphically just how cortical control of older centers is effected and how, through cerebral association centers, older centers are tied into a new behavior pattern. It also shows how intricate are these new neuronic associations or engrams and that these, being specifically human, depend upon an intact neocortex. Karlin's discussion is summarized as follows: A normally developed cortex is essential for speech. The normal activity of the cerebral cortex is dependent upon the interaction of two processes: the sensory and the motor. Myelinization of fibers of the central nervous system proceeds in the following order: (1) the sensory, (2) the motor, and (3) the association fibers. Speech impressions are received in the cerebral cortex by all the senses: auditory, kinesthetic, tactual, visual, gustatory, and olfactory. For the normal development of speech, at least one of these senses, i.e., good hearing, is indispensable, especially in the early periods of childhood. The sphere of hearing in the temporal lobe of the full term newborn infant can be sharply distinguished by its marked myelinogeny in contradistinction to other temporal spheres, and from all evidence the auditory mechanism is well established at birth. The auditory word area is at the upper, sylvian, surface of the temporal lobe and in the adjacent posterior end of the first temporal convolution. The visual word area is the angular gyrus. The auditory word area is connected by association fibers with the motor speech area, Broca's area, located at the posterior end of the inferior frontal convolution and in the adjacent parts of the precentral convolution and of the insula. The visual area is linked with the motor area for writing, which has not been definitely placed. Myelinization of the motor tracts is not complete at birth. Even nine months after birth myelinization of the pyramidal tracts is not complete. At birth the fibers of the olivospinal tract have not even begun to myelinate. Since speech depends upon the functional maturity of both sensory and motor pathways, as well as of the association centers, it cannot begin until myelinization of all components is complete.

There is no peripheral organ or set of organs that has been set aside by nature for the peripheral production of speech. All the structures that are used for articulation have been serving and are serving purposes biologically more fundamental than speech. These are the functions of respiration, mastication, and deglutition.

It is readily apparent, then, that the first truly human neural mechanism to be developed is associated with the functional and structural maturation of areas of the neocortex, and in its development makes use of and modifies lower neuronic patterns. Also, " there is a universal unanimity of opinion

that speech is an index of the mental development of the individual. Mental (intellectual) retardation has to be considered when a child of two and one-half or three years has shown no attempt at vocalization."

Following vocal expression the next step in cortical development is shown by the formulation of coherent sentences, a task which requires development of cortical association patterns involving all sensory components listed above and a complicated and intricate association and motor system. This develops as the neocortex develops structurally.

If we accept the appearance of speech as the first indication of the functional integration of the human neocortex, and, *ipso facto,* as the first indication of intellectual development we can trace the intellectual development of the individual from this stage onward as an expression of the gradual structural and functional maturation of the neocortex and will have established in the human premotor cortex a structural and functional basis for intellectual activity.

It is generally agreed that the human brain is structurally mature at about six years of age, i.e., that the numerical maturation of neurons is complete. From this period until well into middle life development is represented only by a numerical increase in cellular processes (dendrites) and an increase in the number of neuronic associations. The period from the time of the appearance of speech until about six years of age represents the period of structural development of the physical substrate of " conceptual ideation." From six years to physiologic maturity represents that period during which intellectual engrams and concepts of behavior are integrated and consolidated by precept and example, and during which the highest cortical centers are stimulated by experience and instruction toward the ability for thought synthesis, about which more will be presented later.

It is during the formulative period of development, both from a behavior and neurological standpoint, for the two are inseparable, that factors of importance in the understanding of schizophrenia develop.

During this period the individual is not a " free " organism, but is under the guidance of his creators, his parents or their substitutes. It is the period of protective education in the laws of human behavior on one hand, and a period of protective instruction in the mechanisms required for " free " existence in a communal adult society on the other. Of the former we may refer to this phase of development as the inculcation, in the developing mind, through stimulation of neuronic associations by repetition and reiteration, of those idealistic concepts of behavior which have been passed through generations of human existence, modified and amended according to circumstance, and which reflect the experience of the race. In other words, it is during this period that the individual learns the rules of behavior according to the religious, economic, and social ideals of his instructors and through painful and pleasant personal experience. The " instructed " neuronic associations of behavior formed during this period are precepts, not concepts, i.e., the stimuli and the neuronic associations they produce are " from the out-

side" and, if we may use the term, they are mechanical acquisitions. The ability for concept formation at this period is limited and immature and functions only in response to poignant stimuli of pleasure or pain. The biologic purpose of this training is, of course, to prepare for the successful socialization of the individual when he becomes "free."

The sensory-association-motor pathways formed through neuronic associations depend for their consolidarity upon one of two factors, both of which are continuously operating during the formulative period of development. On one hand we have stimuli constantly repeated and nervous energy flow over the same neuronic chains. On the other we have stimuli arising from a situation which is so poignant and intense that consolidation and integration of a high functional degree are effected immediately. Thus a child may be repeatedly told never to put its hand in a flame and eventually learn never to do so. Another child may never be so instructed, but once experiencing the pain of such an act, will never again perform it and will have a painful recollection of his experience to guide him through life. Therefore, experience and instruction (thus, total environment) play a major rôle in determining the behavior of an adult through the strength of the neuronic patterns they integrate during the formulative period and must be given major consideration in the interpretation of functional disturbances in the adult nervous system. We find that these are mechanical reactions which function more or less as closed circuits in which evaluation of circumstances does not enter into the response. Intensive religious training is an example of this. We may also explain it as an acceptance of facts without an evaluation of the total perspective of forces brought into synthesis in the formulation of behavior responses. It is the mechanism which underlies delusions in pathologic states, and is associated with a stage of neural development corresponding to that found in the formulative period of development. During this period "precept" behavior is the dominating neural mechanism in behavior although "concept" behavior is developing as the individual approaches physiologic maturity.

We may summarize the development of the human nervous system postpartum in another way, paraphrasing Jelliffe: In infancy both the level of intelligence and the products of intelligence (ideals) are weak and unorganized and the phylogenetically older levels are all powerful. The child lives in a phantasy world with its primitive pleasures. He has tantrums, or sulks, or cries when not satisfied, and laughs and gurgles when pleased. He mostly sleeps. Through pain and pleasure the intellectual or conscious level begins to learn about reality, and then through precept and example builds up its own nervous pathways as adaptations to the world. The unconscious phylogenetically older centers become guided by conscious experience, and still further controlled by the refinements of civilization (ideals) to such a degree that behavior is made comfortable to the mores in each particular situation, i.e., ideally becomes adaptive, successful, and pleasure giving. (Thus the older levels become sublimated and their forces become socially

creative and attain survival value, both individually, racially, and sociologically.)

Man becomes physiologically mature at puberty, i.e., he is capable of mating and of reproducing his kind. The sexual urge in all lower forms of life reaches an intensity which demands satisfaction at the time of physiologic maturity. In the human organism this urge may be somewhat less intense at this physiologic period, but is nevertheless of sufficient intensity to arouse a mating instinct and to urge the individual to gratification. However, in a civilized state, through species experience and economic, social and other environmental circumstances contingent upon the instincts of gregariousness and moral obligation, there is a general agreement among individuals that the ideal age for mating is not at puberty but later in life, and that mating and reproduction must be consummated only according to certain sets of idealistically conceived laws. The necessities of communal existence on a civilized plane demand this, and in the developing individual nervous system, because of its general necessity, these "ideals" are inculcated through education, an education which consists of instruction by constantly repeated verbal stimuli, taboos, and stimuli associated with religious pageantry. Fundamentally it is an attempt, for the biologic purpose of species maintenance, to readjust a basic biologic urge and its physiologic counterparts to a pattern of behavior which is based not on an individualistic scheme but on the instincts of gregariousness and moral obligation by developing a dominance of neocortical neural mechanisms over phylogenetically older neural mechanisms and modifying these mechanisms to conform to the newer concepts. Non-technically it is an attempt by the intellect to accomplish a complete dominance of human ideals over animal instincts.

Obviously this attempted readjustment of the organism is not completely effected. If man were phylogenetically mature the dominance would be effected; i.e., through the consolidation and integration of neocortical neuronic patterns and their functional dominance of older instinctive patterns these older patterns would be modified to conform to those patterns of behavior conceived, formulated and now only fairly well consolidated in the neocortex in response to the demands of a gregarious type of existence based upon moral obligation. But because the race is in an experimental stage of development the "ideal" type of behavior has not been fully determined, and neocortical dominance and modification can not be completely effected until a stable and universally specific engram is determined. Only then can lower neuronic patterns be completely modified. Therefore, when the individual reaches physiologic maturity two antagonistic forces are brought into play in the determination of his behavior and he is immediately thrown into a sexual conflict. On one hand he is subject to a basic biologic urge which demands gratification as an individual, and he has strongly integrated individualistic engrams which he has inherited phylogenetically to accomplish this gratification. On the other hand, he has higher neuronic mechan-

isms, consolidated by species experience and throughout the formulative period of his life, which contradict these individualistic urges, but which are not well enough consolidated by species experience to dominate them completely and modify their function completely to conform to the "higher" demands. This results in the fact that his behavior, with regard to his sexual urges, is a compromise between these two antagonistic urges, and this sexual conflict with all its ramifications is a normal conflict contingent upon man's phylogenetic immaturity.

Much stress has been laid upon sexual conflicts in the pathogenesis of many functional mental disturbances as well as in schizophrenia, and it is for this reason we have indulged in the above delineation. We feel that this conflict is purely neurobiological and based upon man's immature phylogenetic status. However, this same state of conflict, which we have delineated for the reproductive urge, is also present and normal for the urges of hunger and self-protectiveness * and for the same reasons. Without going into detail, for we believe the implication is obvious, this is responsible for all of our political, financial, social, religious and ethical unrest as well as for the eternal conflict between individuals and nations. It represents a conflict between individualistic urges and moral obligation in which sometimes one and sometimes the other plays a dominant rôle in behavior. The point is that this conflict is "normal" and must be met in every situation which arises in our daily lives after we pass the age of physiologic maturity.

How are these conflicts met and how is behavior decided? This is the essential function of the highest centers of the neocortex, those centers concerned with "concept formation" or the centers for conceptual ideation. In every new situation with which man is faced in his daily life he is called upon to form a concept of behavior, through new cortical neuronic associations, which results in a compromise between animal instinct and human ideals. It is the function of the highest cortical centers to analyze the situation, to coördinate past experience with the probable results of the new concept on the future for the individual, and indirectly the race, and to effect a compromise between individualistic urges and moral obligation. In terms of neurodynamics every situation which is new for the individual and of sufficient intensity to require a modification of his past behavior or the formation of a new behaviorism requires the functional integration of new neuronic associations in the neocortex and the functional linkage of these with the parts of the lower nervous system to be called into play or modified in the given situation. Thus, the ability to form new concepts and compromises between animal instincts and human ideals is an indication of the functional integrity of the highest cortical centers. Whether or not the compromise favors the ideals based upon moral obligation, intelligence, or individualistic urges is an indication of the degree of neocortical de-

* Thus explaining Adler's urge to power.

velopment. The satisfactory compromise, from a biologic standpoint, is that which insures successful socialization of the individual.*

Genetic Background

Although the burden of proof, except perhaps in the manic-depressive psychoses, indicates that so-called functional mental illnesses are not directly inherited as such, there are many indications that an "heredity factor" operates in the pathogenesis of such states. Primary mental deficiency, because it exhibits a numerical deficiency of cortical neurons, as well as other directly inherited structural defects of the nervous system, may be excluded from this discussion as not pertinent. We are concerned primarily with those states characterized by a structural sufficiency and a functional inadequacy. The question resolves itself into whether or not the functional potential of cells of similar morphology differs in different individuals, and whether or not the degree of functional potential of the cells of the nervous system is influenced by heredity. This is a question the answer to which must be found in clinical comparisons.

From the fact that within certain families we find a more than coincidental number of individuals who exhibit functional disturbances of the nervous system and who often present a picture of neurosomatic inadequacy we can deduce that in these individuals there is a lowered potential for sustained neural activity. It is also true that in a given trying situation these individuals react inadequately, whereas members of families free or comparatively free of nervous disorders are able to carry on without evidence of functional failure. Hereditary functional inadequacy is noted with regard to other organs and systems, particularly with reference to the kidneys, heart and genital organs, and it does not seem illogical to assume that the functional potential of the cells of the nervous system is determined, in part at least, by heredity and that this must be given consideration in studying the pathogenesis of schizophrenia.

Physiological Background

The neuron is the genetic, structural, trophic, and functional unit of the nervous system. It alone is concerned with the conduction of nervous impulses. Therefore, the functional integrity of the neuron is essential to normal nervous mechanisms. The functional integrity of nerve cells depends upon the continuous inter-reaction of the nucleus and cytoplasm to serve two purposes—to maintain the vitality of the cell and to carry on the transmission of neural energy over its circuit in response to the demands

* Lest this be misinterpreted as a plea for communism or socialism, it is not; in fact, the contrary is true. Communism is moral obligation carried to its idealistic pinnacle, as are the basic tenets of Christianity. But man, as we have attempted to point out, is not phylogenetically mature enough for these doctrines to be practical, for they fail to take cognizance of his individualistic urges, urges too powerful for total subjugation as yet. Their subjugation is a matter of centuries or eons, not years.

of the organism. These functions depend on the availability of metabolites and the functional ability of the neuron to transmute these metabolites into nervous energy. Nervous energy expenditure and repletion, in accord with the universal law of energy, is the ultimate problem of nervous physiology, and, in the ultimate analysis, all behavior from the most simple to the most complex depends upon the conversion of carbohydrate into nervous energy.

Obviously the more work a cell or group of cells is called upon to perform the greater will be the energy requirement and the metabolic rate. There are many ways of measuring this, such as the period of cellular activity which follows isolation of the cell from the source of combustive energy (oxygen), the degree of fatigue, and the duration of the period of energy restitution, measurements of oxygen consumption, etc. These studies indicate definitely that the highest metabolic requirements are found in the cells of the cortex. This is readily explainable if we analyze behavior patterns as they reflect the neuronic level of function with which they are associated.

Reflex patterns of behavior involve nervous energy transmission over neuronic circuits involving relatively few neurons, which are inherited by the individual, established early, phylogenetically consolidated, and well integrated by continuous and frequent use. The barriers to impulse transmission are minimal. Repeated use of any neuronic circuit, once established, involves less and less energy as consolidation increases. This is well exemplified by the effort required to learn precepts and behavior patterns early in life which function with such facility once " learned " that conscious effort is not required later in life for energy flow over these circuits. The formation of concepts involves polarization of the cell body, extension of dendritic processes, and synaptic coördination of these processes with those of cells or cellular groups involved in the total reaction pattern. This is the most energy depleting process the nervous system is called upon to perform.

We may, therefore, postulate general levels of energy demands. From the lowest level of simple reflexes, requirements for function increase through the higher reflex levels, instinctive levels (phylogenetic mnemic levels), human instinctive levels, patterns " learned " in the formulative period of development, concepts formed by the individual, to the level of active concept formation.

It follows that the function of the highest levels requires an adequate source of energy as well as the functional integrity of the cells of the neocortex involved in the formation of concepts to maintain normal human behavior.

We have outlined *above* certain backgrounds which we feel are essential to an understanding of the neuropathology behind the schizophrenic process. Each supplements the other and is a factor of importance, there being no one specific factor which is totally explanatory per se. The data presented may seem unrelated taken separately, but a study of the manifestations of schizophrenia, as well as those organic states which are capable of producing those

functional aberrations seen in schizophrenia, makes a correlation of these data possible.

The Schizophrenic Reaction

The schizophrenic reaction may be initiated as a unique and relatively sudden change in a previously "normal" individual, it may evolve slowly from a mild or severe neurosis, or it may be superimposed as a culminating disaster upon an inadequate personality. However, its genesis, the primary universal manifestation from a behavior standpoint, is socialization failure. The patient stands apart from the majority to the extent that his behavior is noticeably "peculiar." The individual is no longer "one of us," but an abnormal personality unable to be successfully socialized. Many terms have been given to this earliest and universal manifestation of the reaction: personality distortion, personality isolation, personality disintegration, personality deterioration, unadaptable personality, and shut-in personality. The victims are called social misfits and they have been described as socially useless. They are frequently characterized as "extremely vulnerable to the hurts of the world" and are said to have withdrawn "from reality into phantasy." It is said that their behavior is due to "substitutive reactions," and that they are "dodging reality." The latter terms too often imply or are interpreted as indicating a willful reaction on the part of the patient, a conception with which we do not hold and which we feel is biologically unsound.

As the reaction progresses beyond this "incubation period" of socialization failure, evidence of a more pronounced psychologic or physiologic disturbance appears. The socialization failure becomes so marked that isolation from "normal" humanity often is required and behavior is overtly bizarre, the individual becomes useless to or detrimental to his community, occasionally a dangerously atavistic personality. He reacts to life as an individual and not as a member of a communal society. His obligations are only to himself. The psychiatrist finds that there is an illogical or incoherent association of ideas, thought deprivation, infantile cerebration, inconsistent thinking, faulty judgment, a loosening of association systems, emotional disturbances, attention difficulty, and a preoccupation with his own ideas, a withdrawal from the circumstances of the environment. The mental content is found to be dominated by false ideas or delusions, and insight is lacking. The patient is found to be unable to synthesize data into normal concepts of behavior; the association systems are disturbed. An analysis of the cerebration of the schizophrenic points to one universal finding which underlies all other manifestations of the process—the patient is unable to form those concepts which are required for socialization success; he has primarily a defect in the sphere of conceptual ideation, i.e., this level is excluded from the total reaction of the nervous system.

Levin's [5] analysis of the manifestations of schizophrenia bear out this

premise, i.e., the premise that schizophrenia results from a reaction pattern in which the highest cerebral centers (those concerned with "conceptual ideation") are non-functional. He concludes: "In schizophrenia . . . there is a loss of cerebral 'versatility' resulting in fewer and less complex concepts and in diminished capacity to differentiate concepts. There is a loss of autonomy of the cerebral parts . . . and an increased tendency to mass reflexes." By example he shows how closely the neurodynamics of schizophrenia approach the neurodynamics of the nervous system of an infant during the period when its nervous system is anatomically immature, i.e., before cerebral neuronic development is complete.

Socialization failure and a loss of ability for conceptual ideation are the two universal manifestations of the schizophrenic reaction and are obviously inter-related, the one the overt representation of a physiologic disturbance in the highest cerebral centers.

The other manifestations of schizophrenia vary both in degree of severity and in type. The intellectual deficit may progress to the point of almost total amentia, and the patient presents a picture commensurate with that seen in severe organic disease of the nervous system. Marked disturbances of the autonomic nervous system occur as in catatonia, symptoms suggestive of hypothalamic involvement. Emotional disturbances may become marked with either emotional blunting, emotional inconsistency or euphoria dominating the picture. In some cases deterioration is progressive and in others the picture remains almost stationary for years. Delusions may be well-fixed and systematized or may be bizarre, variable and poorly systematized. Hallucinations may or may not be present, or if present may disappear or change in their form or in the sensory field in which they are experienced. Some patients may recover from an initial attack and never experience recurrence; others may have several attacks with remissions, and others may never recover from an initial attack.

The manifestations are so variable and unpredictable, indicating everything from the most mild to the most severe involvement of the nervous system, that one is led to believe that the term schizophrenia does not characterize a disease entity but a group of disturbances of the nervous system in which there is some similarity between basic symptoms, but which are physiologically related only as the diseases of the heart which produce cardiac decompensation are related. The analogy may be reversed. Just as any disease process capable of interfering with the normal metabolism of the heart muscle will produce cardiac decompensation, any factor which is capable of interfering with the metabolism of the cells of the higher levels of the nervous system is capable of producing the manifestations of schizophrenia, and the degree of severity of the process will determine the physiologic level to which the nervous system regresses. When we find some morphologic change in the cells of the nervous system as in senile psychoses, luetic infections, cerebral trauma, hereditary neuronic deficiencies of the

cortex, or tumors we do not call the illness schizophrenia even though the manifestations may be indistinguishable from those seen in schizophrenia.

Let us consider for a moment primary mental deficiency in which there is an actual deficiency of neurons in the premotor cortex. The behavior and test patterns of these cases show greater predictability, consistency, and leveling in test strata than any secondary types of mental deficiency, and we know that we are dealing with a reaction pattern in which those centers concerned with the higher levels of concept formation are inadequate. In the high moron or borderline cases we note the following differentials between the behavior of these patients and the "normal" person:

1. An inability to form concepts, i.e., an inability to synthesize past experience and new perceptual phenomena into new association systems which adequately meet the demands of society; an inability for conceptual ideation of a high order.
2. A deficiency in judgment, primarily a manifestation of the above inadequacy.
3. A lack of idealistic supervision of the sexual urge.
4. A definite predominance of individualistic drives over communal drives.
5. A deficient sense of moral (sociologic) responsibility.
6. A juvenile type of cerebration.
7. Emotional inadequacy.
8. Socialization failure dependent upon an inability to adequately meet the intellectual demands of communal existence.

We find here the *basic* manifestations of the schizophrenic process, the difference being that in one case the manifestations are obvious from early infancy and in the other they develop in an individual who once presented a picture of normal or relatively normal mental development and behavior.

The author recalls to mind cases of post traumatic psychosis in which the patients presented a typical schizophrenic reaction and in which autopsy revealed cellular destruction in the higher cortical centers. He has had cases of senile dementia which in a younger individual would have been diagnosed schizophrenia of the catatonic, hebephrenic, or paranoid type as well as a case of syphilitic meningo-encephalitis in a young male in whom the manifestations were so typically catatonic that permission for metrazol therapy was obtained before the Wassermann and spinal fluid findings proved the true basic pathology. Every psychiatrist has seen cases of organic disease of the nervous system in which the diagnosis could well be schizophrenia if *there were not a definite etiologic factor to account for the change in personality and behavior.*

To what does this lead us? Only to the conclusion that the study of any mental disease must follow the scientific postulates of the study of any somatic disease and must be referred ultimately to the question of a dis-

turbance in the physiologic processes of the cells of the organ which is being attacked. The study of the schizophrenic reaction is not a matter of classifying symptoms and indulging in philosophical speculation as to their import, but in attempting to evaluate these symptoms in the light of the development, form, and function of the nervous system. Although the products of function of the nervous system, behavior and thought, are not measurable in milligrams per cent they are nevertheless a manifestation of the energy production and expenditure of the cells of the nervous system and must be so interpreted and evaluated.

Synthesis

Assuming, as we do, that the schizophrenic reaction is the result of a disturbance of the normal function of the cells of the nervous system, we have certain tangible facts which, although they do not necessarily point to the specific etiologic factor, indicate the nature of the forces at work which result in this functional disturbance.

Much stress has been laid upon the "conflict situation" as an etiologic factor. We have attempted to show that the "conflict situation" is a normal situation to which every percipient being is subjected from the time he reaches physiologic maturity until such time as he is no longer called upon to adjust himself to his environment as a "free" being, and that these conflicts are the direct result of man's immature phylogenetic status. The eternal conflict between individualism and moral obligation in the determination of man's behavior in response to the biologic urges of hunger, self-protectiveness, and love is the universal heritage of man. If we are searching for the causes of mental illness we must go deeper.

We have further attempted to show that man's species-specific mechanism for adapting himself to his environment in such a manner as to best serve the biologic goals of life is a uniquely human cerebral cortex, the cells of which are not mature at birth and the development of which is progressive from birth to senility. The highest and most intricate and involved function of this cortex is the formulation, through neuronic associations, of concepts which compromise individualistic urges and the urges of moral obligation and result in behavior acceptable to the mores. In delineating the physiology of levels of nervous function, we have seen that the level of concept formation requires the greatest energy potential and energy supply of all levels of function, that old concepts, once established, function with less expenditure of energy, and that phylogenetically established circuits require less energy for function than higher cortical circuits.

In evaluating the symptomatology of the schizophrenic reaction we find that there is one universal manifestation, an inability to form those concepts of behavior which normally adjust the individual to his environment as a member of a communal type of existence. We find, also, that the schizophrenic's behavior reflects a juvenile type of mentation in its less

serious form and a distinctly atavistic and unhuman type of behavior in its severe form, and that the reaction pattern reflects a neurodynamic state found in childhood when the nervous system is anatomically and physiologically immature, i.e. when the cells of the highest centers of the cerebral cortex are not developed. The severity of the process determines the degree of return to lower functional levels, i.e. delusions follow in general the type of reaction found in the formulative period when "precept" rather than "concept" mechanisms are in play (i.e. there is an incomplete synthesis of data) and incoherent thought processes mark a return to a juvenile level near or at that stage of nervous function when vocalization is possible but is incoherent. (The gradual return through fixity of thought to incoherent speech seen in progressive alcoholic saturation which gradually eliminates cortical function from the highest levels downward also exemplifies this "cutting out" of cortical dominance.)

We also found that the schizophrenic reaction is so variable in its superficial manifestations that one is led to believe that schizophrenia is not a disease entity but a grouping of illnesses with one common manifestation just as one groups various entities under the term mental deficiency. We find as well that organic destruction of the cells of the cerebral cortex, and those phylogenetically newest are most vulnerable to attack, results in a reaction often indistinguishable from the schizophrenic reaction.

From these observations we conclude that the schizophrenic reaction results from a basic metabolic disturbance of the cells of the cerebral cortex which excludes or depreciates the ability for concept formation from the total reaction pattern of the nervous system, and results in a more juvenile or atavistic reaction to the circumstances of the environment. We do not feel that the "withdrawal" from reality is a willful mechanism, but that it results from an inability to adequately adjust to reality because of a physiologic deficit in the highest levels of nervous function, and that the type of behavior noted, juvenile or atavistic, reflects the highest level of nervous activity of which the organism is metabolically capable.

What then produces this metabolic deficit?

In any system, mechanical or physiological, in which several units function in reciprocal arrangement, that unit which is weakest, most unstable, or subject to the greatest stress will be the first to break down under great stress, or will be the first to manifest malfunction if other units fail to carry on their specific functions by not contributing their full share of work to the total mechanism. In the hierarchy of organs and systems which constitute the human organism, the nervous system is the unifying factor in the total reaction, dominating and coördinating all organ activity and at the same time being supported by and depending for function upon the functional integrity of the units it controls. The "master" of the human nervous system lies in the highest centers of the cerebral cortex. From a biologic and functional standpoint the cells of the human cerebral cortex,

particularly those of the highest functional centers in the pre-motor areas, are the most vulnerable to attack, are the most unstable, and are subject to a greater stress than are the cells of any other part of the nervous system. Therefore, the malfunction of these cells may result from any one of three specific factors—a lack of functional potential (hereditary cellular weakness), direct attack by a destructive force, or a disturbance in the function of some other unit of the organism upon which these cells depend for their metabolic requirements. Further, the breakdown of function is most likely to occur at that period when these cells are called upon for their greatest effort, i.e. when the circumstances of reality result in serious conflicts which require the integration of many neuronic units into an adequate concept to solve the problem presented by the situation.

Those in close contact with schizophrenia are impressed by several distinct observations in case studies. It is seldom that in taking a history one is unable to unearth a conflict situation which may be considered a precipitating factor in the psychosis and to which members of the patient's family refer as the "cause" of the patient's "breakdown." Also, one is impressed by the unusual frequency of a history of an inadequate personality or constitution in the background of the patient previous to the actual development of the psychosis and the gradual evolution of the psychosis precipitated by a specific conflict situation. We may eliminate as an etiologic factor the conflict situation, for as we have seen such conflict situations are universal and do not always result in a psychosis when they occur. In the individual case, the conflict situation may be the precipitating factor, but is not the etiologic factor.

Cardiologists speak of cardiac compensation, work reserve and decompensation and refer directly to the functional potential of the muscle cells of the heart. They find that many hearts are functionally capable of carrying on under normal stress and demands, but have no reserve power to take care of excessive demands caused by physical strain. The heart then decompensates, i.e. the muscle cells fail to adequately carry on. We find the same mechanism in schizophrenics. Most frequently this psychosis develops in individuals who seem to be functioning at their "peak performance" level in meeting the ordinary situations in life, and when a serious conflict situation arises they lack the reserve to carry on under the added demands on the highest functional level of the nervous system. The "breakdown" is then manifested by a functional inadequacy of the cells of the highest functional centers of the cerebral cortex, those requiring the greatest energy supply and expenditure for adequate function, and the result is the schizophrenic reaction in which lower and less energy demanding levels of function dominate the reaction of the organism. On the basis of this interpretation we may say that of the forms of schizophrenia the paranoid reaction is the least severe and the catatonic the most severe form of functional breakdown, for

in the former the return to lower levels is least marked whereas in catatonia * the manifestations indicate a regression to the diencephalic level of control. It must be remarked that the diencephalon (hypothalamus), upon which so much emphasis has been recently placed, does not control the cerebral cortex, but is a "distributor for a more comprehensive hook-up" in which the cerebral centers are normally the point of impulse initiation. Obviously, if the cortical centers are not in full functional control, the hypothalamus will be released, partially or completely, from cortical control and manifestations of hypothalamic dominance will occur. In the least severe forms the return will be to a juvenile type of mentation, a less energy demanding level, and childhood † or juvenile engrams and mechanisms will be brought into greater dominance in the total reaction. Infantile impressions and training are not etiologic factors, but may serve to intensify the conflict in any given situation or may color the delusional pattern. Delusions in themselves indicate that the nervous system is functioning at a juvenile level. *The return to infantile or juvenile reactions is not purposeful but is a physiologic necessity.*

A second finding is less frequent than that of personality or constitutional inadequacy; namely, the history of some somatic illness occurring as a precipitating factor in the development of the schizophrenic reaction. Here the pathogenesis should be obvious: a debilitating illness which deranges metabolism and homeostasis, the point of functional inadequacy developing at the weakest point in the entire structure—the cerebral cortex.

Less frequently we find the schizophrenic reaction developing in an adequate personality in which there is apparent no somatic deficiency factor to explain the reaction. The "conflict situation" will be elicited almost without fail, and the "break" is usually acute. We can explain this only as a direct functional depletion of the potential of the cells of the cortex in response to the excessive demands of the situation.

In other organs, e.g. the pancreas, functional derangements in the cells often result in permanent and progressive destruction or may be temporary. If we apply this same physiological fact to the cells of the nervous system we have a rational explanation upon which to interpret the fact that the prognosis in schizophrenia is so variable. It explains the progressive deterioration, suggestive of organic damage in some cases, the temporary duration of the psychosis in others, and the repeated attacks with remissions in others.

Conclusions

A correlation of data presented leads us to the conclusion that the schizophrenic reaction results from a basic metabolic disturbance of the neurons

* The intact sensorium in many catatonics does not controvert this argument but strengthens it. The sensory mechanism may be intact but the association centers are unable to respond sufficiently to affect motor response.

† Precepts and delusions, because of the fixity of their circuits and the fewer neurons involved, require less energy expenditure for function than concepts which require polarization of new neurons and a greater number of neurons for inclusion in the circuit.

of the cerebral cortex, that the biologic factor in the pathogenesis of the reaction is man's immature phylogenetic status, that the hereditary factor is the determining factor in the development of the reaction, and that the developmental (environmental) factor determines in part the manifestations of the reaction. We further conclude that schizophrenia is not a specific disease entity but a reaction pattern which may result from any cause which directly affects the functional potential of the cells of the cerebral cortex and that in the main there are three specific mechanisms which will produce the reaction:

1. An inadequacy state with lowered functional potential of cortical neurons in which the organism must function at full functional potential to carry on in the face of the ordinary stress and strain of life and in which there is no reserve for serious emergencies.
2. Debility of the cortical neurons brought about by some abnormal somatic process.
3. Depletion of the functional potential of the cortical neurons.

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PLASMA CREATININE DETERMINATION AS A TEST OF LOW GRADE KIDNEY DAMAGE*

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Whereas there are well established methods of determining definite kidney insufficiency, the detection of low grade kidney damage by simple methods is still a problem. The purpose of this study is to show the value of plasma creatinine determination by newer methods, in the solution of this question.

In kidney damage the glomerular function is usually the first to be impaired as indicated by reduction of glomerular filtration. The original method of Rehberg [1] who used the exogenous creatinine clearance as a measure of glomerular filtration has been discarded, since in man creatinine is secreted when the blood level is artificially raised.[2] The inulin clearance is now considered the most reliable measure of glomerular filtration. The endogenous creatinine clearance [4] gives similar results.[5] Despite criticism of the theoretical value of the endogenous creatinine clearance as a measure of glomerular filtration [6] its determination may be of clinical importance because of the simplicity of the technic.

Since endogenous creatinine is filtered through the glomerular loops and is probably under normal conditions neither secreted nor absorbed in the tubular part, any disturbance of the glomerular filtration causes retention of creatinine in the blood. The glomerular filtration undergoes physiological variations, whereas the blood creatinine level remains relatively constant.[7] For clinical purposes, therefore, the blood creatinine determination is as informative as, and in some respects superior to, the time-consuming determination of glomerular filtration. A mild reduction of the urea filtration is compensated by reduction of the physiological urea reabsorption in the tubules. A reduction of the creatinine filtration cannot be compensated.

Some changes in the chemical technic and the use of newer optical instruments (examination by monochromatic light) have rendered the colorimetric determination more sensitive; an accurate determination at the normal blood level is now possible.[8] In low grade renal insufficiency the results obtained are for this reason not in agreement with those obtained by older methods.

There is a disagreement as to the nature of the substances in the blood giving the creatinine color reaction.[9] There is, however, some creatinine present under normal conditions. The amounts found with the new method are in agreement with those obtained by more specific reactions.[10] Some

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results obtained with this method have been published.[11] The following study substantiates these results.

Method[8] and Material

Reagents: (1) Saturated picric acid solution. The picric acid crystals are purified according to Benedict.[12] (2) 10 per cent sodium hydroxide, chemically pure.

Four c.c. of oxalated plasma are added drop by drop to 12 c.c. of picric acid. The test tube is shaken and immersed in a boiling water bath for 15 seconds. The mixture is filtered through a Whatman filter No. 44. To 10 c.c. of the cooled filtrate 0.5 c.c. of sodium hydroxide is added. The mixture is filtered again through another Whatman filter to clear additional turbidity. The colored solution formed is read with monochromatic light with a filter of 530 millimicron 20 minutes after the addition of sodium hydroxide. The determination is made with either (1) a colorimeter, with artificial light and with a gray solution (Leitz) as a standard (depth of column of the unknown is 50 mm.); or (2) with a photometer (depth 60 mm.; instead of plasma, water added to picric acid and sodium hydroxide is used for compensation); or (3) with a photoelectric colorimeter.[13]

Using a known creatinine solution, a comparison curve is made in the range between 0.5 and 3.0 mg. per 100 c.c. If the creatinine concentration exceeds this range the plasma is diluted with water. The normal level lies between 0.60 and 0.95 mg. per 100 c.c. It is constant in normal individuals on different days or different times of the day. Food or fluid intake is without influence. Any increase over 1.0 mg. per 100 c.c., even as slight as 1.05 mg. per 100 c.c., is a probable sign of disturbed glomerular filtration.

The material consists of 278 patients, many of them examined several times (474 examinations). In the table the cases are recorded with the highest creatinine level obtained. Patients without kidney disturbances or without diseases commonly associated with extrarenal azotemia are not included in this study. The creatinine concentration in the plasma of normal individuals has been reported previously.[11]

Findings

Acute Glomerulo-Nephritis. The 26 patients with acute glomerulonephritis show different stages of the disease (table 1). In 74 per cent an increase of the creatinine level over the normal was observed and only in one case did the level exceed 1.40 mg. per 100 c.c. In 7 cases the return to normal was followed, whereas in the other cases with increase only single examinations were available. The fact that in many cases a normal creatinine level was obtained and in others a decrease of the creatinine was observed led to an average of 1.05 mg. per 100 c.c.

TABLE I

Plasma-Creatinine Values in Pathological Cases

Diagnosis	Number of Cases	Number of Examinations	Maximum Creatinine, mg. %	Minimum Creatinine, mg. %	Average Creatinine, mg. %	Percentage of Cases with Blood Creatinine		
						Below 1 mg. %	1 to 1.4 mg. %	Above 1.4 mg. %
Acute nephritis	26	56	1.44	.45	1.05	26.9	69.2	3.9
Extraglomerular acute nephritis	1	2	37.10	37.10	37.10	0	0	100.0
Transitional stage between acute and chronic nephritis	3	3	2.60	1.33	2.16	0	33.3	67.7
Acute exacerbation of chronic nephritis	2	5	24.80	1.14	9.36	0	0	100.0
Chronic nephritis	33	67	26.08	1.01	6.06	0	18.2	81.8
Nephrosis	12	27	2.60	.62	1.32	16.7	66.7	16.6
Amyloidosis	1	1	1.76	1.76	1.76	0	0	100.0
Benign nephrosclerosis	73	115	4.20	.49	1.24	34.2	34.2	31.6
Malignant nephrosclerosis	24	43	17.10	1.15	4.18	0	8.3	91.7
Polycystic kidneys	1	3	1.99	1.89	1.94	0	0	100.0
Obstruction of urinary passages	19	40	15.85	.80	4.95	15.8	15.8	68.4
Pyelitis	9	12	1.07	.76	.89	77.8	33.2	0
Extra-renal azotemia heart failure	26	35	1.91	.70	1.05	38.2	46.3	15.5
Pneumonia	5	5	1.22	.45	.98	60.0	40.0	0
Liver disease	27	34	16.52	.56	2.15	33.3	29.6	37.1
Hypochloremia	9	15	7.60	.76	1.95	11.1	33.4	55.5
Diabetic acidosis	5	5	4.28	1.04	2.58	0	20.0	80.0
Miscellaneous	2	6	3.36	.93	1.50	0	50.0	50.0
Total	278	474						

The non-protein nitrogen in all these cases was normal or just above the upper limit of normal. All cases recovered clinically.

In one case of acute extraglomerular nephritis with rapid downhill course a very high creatinine level was observed. Here the postmortem examination revealed extensive proliferation of Bowman's capsule with compression of the glomerular loops. In three cases of acute nephritis in which the transition to the chronic stage was observed the creatinine was much higher than in the cases with complete recovery, the average being 2.43 mg. per 100 c.c.

In several cases the creatinine elevation was concomitant with a normal blood pressure.

Chronic Nephritis. In all cases of chronic nephritis an elevation of the creatinine level was found, up to 26.08 mg. per 100 c.c. In 18 per cent of the cases a moderate creatinine elevation was present, with a very slight increase in the non-protein nitrogen; a normal blood pressure and only a few red cells in the urine. In two cases of acute exacerbation of a chronic nephritis the creatinine increase was marked.

Nephrosis. In 10 of 12 cases of nephrosis a moderate increase of the

creatinine level was seen (average 1.32 mg.) whereas the non-protein nitrogen and the blood pressure were normal. Clinically, no difference between these and the two cases with normal creatinine was noted. One case of amyloidosis revealed a high creatinine level.

Nephrosclerosis. One third of the cases of benign nephrosclerosis showed a normal creatinine, another third a moderate increase of the creatinine level. In the remainder the creatinine was above 1.4 mg. The first group revealed normal non-protein nitrogen; the second normal or borderline figures. In malignant nephrosclerosis the creatinine increase was much higher and present in all cases. The average was 4.18 mg. per 100 c.c. in contrast to 1.24 in benign nephrosclerosis.

Urologic Conditions. In one case of polycystic kidneys a moderate increase of the creatinine was encountered. In most of the cases of obstruction of the urinary passages such as nephrolithiasis, prostatitis, and pyelonephritis, a definite increase of the creatinine level was found. In pyelonephritic contracted kidney the creatinine increase was as marked as in the primary or the nephritic contracted kidney. In pyelitis a normal value or slight increase was found.

Extrarenal Azotemia. In this group cases were gathered with signs of nitrogenous retention but without obvious kidney pathology. In decompensated heart failure or pneumonia a moderate creatinine increase was observed. There were other cases of acute hepatitis, cirrhosis, or of obstructive jaundice of long duration which usually showed a definite creatinine elevation. An associated kidney involvement, however, has to be considered in a number of cases.

Instances of hypochloremia were observed associated with pyloric and intestinal obstruction, gastroenteritis with diarrhea and vomiting, and carcinoma of the pancreas. The increase of the creatinine level was evident in these cases although it was not as striking as the non-protein nitrogen increase.

In diabetic acidosis a creatinine increase was seen. The chemical determination, however, was less reliable, since acetone and acetoacetic acid may increase the color reaction.[5]

Under the miscellaneous group a case of Hodgkin's disease and one of bleeding peptic ulcer were included, each showing a moderate creatinine and definite non-protein nitrogen increase.

Creatinine and Non-Protein Nitrogen of the Plasma. In figure 1 creatinine and non-protein nitrogen are plotted against each other. For the normal cases we refer to a similar graph in our previous study.[10] In the range over 1 mg. of creatinine per 100 c.c. many cases were found with normal non-protein nitrogen, indicating the greater sensitivity of the creatinine test. In the cases with more marked creatinine increase there is a difference between renal and extrarenal azotemias. In renal azotemia the creatinine increase is much higher in comparison with the non-protein nitrogen increase,

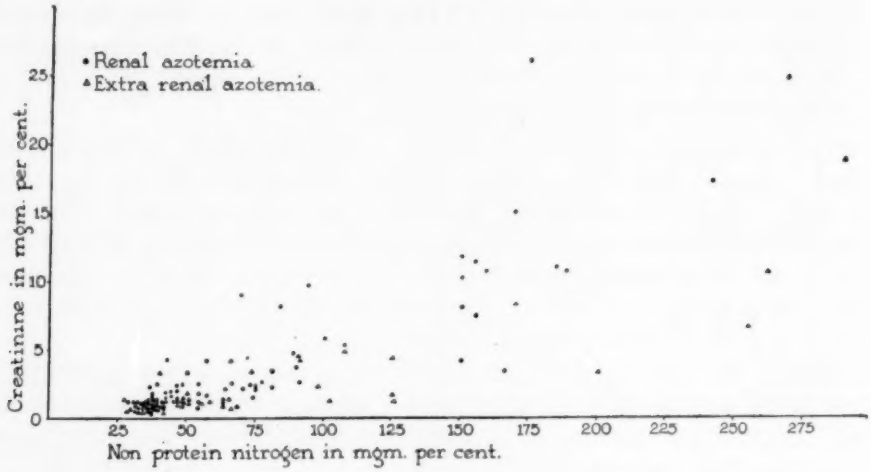

FIG. 1.

than in cases of extrarenal azotemia. The few cases of extrarenal azotemia with relatively high creatinine increase were patients with jaundice in which a nephritic component was either suggested clinically or proved at autopsy.

Relation of Plasma Creatinine to Hypertension and Albuminuria. The plasma creatinine usually runs parallel with the blood pressure and the degree of albuminuria (table 2) in the cases of hypertensive kidney diseases (essential hypertension, benign and malignant nephrosclerosis). In the other pathological cases (nephritides, urologic conditions, extra-renal azotemia)

TABLE II

Correlation between Plasma Creatinine and Blood Pressure or Albuminuria in Pathologica Cases. The Hypertensive Kidney Diseases are Separated from the Other Cases.

Hypertensive	Number of Cases	Maximum Creatinine	Minimum Creatinine	Average Creatinine
B.P. below 150	1	1.02	1.02	1.02
B.P. between 150–180	7	2.32	1.12	1.40
B.P. between 180–220	28	17.1	.59	3.27
B.P. above 220	11	15.0	1.08	4.00
Urine—0	9	2.50	.59	1.82
Urine—One Plus	15	8.35	.60	2.34
Urine—Two Plus	9	11.30	1.15	2.56
Urine—Three Plus	14	17.10	1.02	4.66
Non-Hypertensive				
B.P. below 150	40	16.52	.45	2.93
B.P. between 150–180	12	10.85	.69	2.52
B.P. between 180–220	14	24.80	.78	4.76
B.P. above 220	4	26.08	2.03	10.07
Urine—0	14	4.22	1.01	1.47
Urine—One Plus	18	16.52	.45	3.70
Urine—Two Plus	15	8.45	.62	2.43
Urine—Three Plus	24	26.08	.86	5.48

with and without hypertension, this parallelism is not so obvious except that high grade hypertension is usually combined with very high creatinine levels.

Discussion

The clinical value of the plasma creatinine determination lies in the low ranges; the increase probably indicates a slightly disturbed glomerular filtration. The test in these ranges is superior to the determination of the non-protein nitrogen and urea not only for theoretical reasons (lack of reabsorption in the tubules) but also because of the sharper limits between normal and pathological range, and because of the lesser influence of extra-renal factors such as alimentary intake or protein breakdown.

In the following instances the demonstration of mild glomerular filtration damage is of diagnostic importance:

(1) In acute glomerulonephritis the slight creatinine increase may be helpful in the diagnosis, although a normal creatinine level does not exclude the diagnosis. The creatinine increase is especially significant in oligosymptomatic forms. It may be an early sign of acute nephritis and has the same diagnostic significance as hematuria, edema, or hypertension. It should be sought in the convalescent stage after tonsillitis or other acute infectious diseases. The degree of the increase is significant. If the level lies above 1.4 mg. per 100 c.c. the probability of a transition into a chronic nephritis is present. An extreme increase speaks for extraglomerular nephritis with poor prognosis as to life.

(2) In some mild forms of chronic nephritis with otherwise unexplained albuminuria, headaches or slight anemia, but without hypertension, concentration impairment, or definite non-protein nitrogen increase, the slight creatinine elevation may be helpful in classifying the case. The diagnosis of chronic nephritis may instigate a search for a suppurative focus.

(3) According to the newer theories of nephrosis [14] a changed glomerular permeability is the underlying pathological process (membranous nephritis). The morphological changes in the tubules are secondary, due to reabsorption of proteins and fats which have escaped through the damaged glomeruli. In most cases the nephrosis is a consequence of a nephritic process with at least transitory impairment of the glomerular filtration (proliferative nephritis). The filtration damage is usually not extensive enough to cause non-protein nitrogen or urea increase, but is indicated by slightly elevated creatinine. Only a few cases of nephrosis are absolutely free of any nephritic symptoms, as shown by normal creatinine levels. The creatinine determination is more sensitive than that of urea or of non-protein nitrogen in the detection of a nephritic component in nephrosis.

(4) In the hypertensive kidney diseases the creatinine determination permits a differentiation between the essential hypertension without kidney involvement and the benign nephrosclerosis with slight kidney involvement. In the latter type the glomerular function damage and the impaired blood

flow may be due to primary vascular changes in the kidney or to cardiac decompensation. In decompensated cases successful cardiac management decreases the creatinine level.

(5) In urologic conditions the creatinine increase is an early sign of parenchymatous kidney damage.

(6) In extrarenal azotemias two possibilities are present. First, a moderate creatinine increase with normal or nearly normal non-protein nitrogen as seen especially in decompensated heart failure, with consequent improvement after successful cardiac management. The slight glomerular filtration damage is due to reduced blood flow. A reduction of the urea filtration is compensated in contrast to that of creatinine. The creatinine elevation indicates the degree of congestion in the kidney. A differentiation from similar creatinine increases in acute nephritis, nephrosis, or benign nephrosclerosis is nearly always possible with the help of other findings.

In a second group of diseases usually associated with extrarenal azotemia, such as hypochloremia, liver diseases, or diabetic acidosis, the increased non-protein nitrogen is out of proportion to the normal or slightly increased creatinine. The hypothesis may be offered that the filtration damage is less significant than a pathologically increased reabsorption of nitrogenous substances through the damaged tubules. The backflow of urea is more extensive than that of creatinine.[15] In nephritis the functioning nephrons reveal intact tubular epithelium, consequently the reduced glomerular filtration is compensated by reduced tubular reabsorption.[10] In extrarenal azotemia, fairly normal glomeruli are connected with damaged tubules (e.g. icteric nephrosis) and a reabsorption uremia is possible (disorganization of kidney function in diabetes.[17])

Except for these already known differences [18] between renal and extrarenal azotemia, the creatinine determination offers no advantages over the determination of other nitrogenous substances, in the higher creatinine ranges. The theoretical objections against the endogenous creatinine clearance as a measure of glomerular filtration are especially valid for the high creatinine ranges in which reabsorption or secretion of creatinine in the tubules may be considered.

Summary and Conclusions

The application of a new simple determination for plasma creatinine provides a helpful diagnostic procedure for the detection of mild disturbances of glomerular filtration and, consequently, of low grade kidney damage. The demonstration of these disturbances is of diagnostic and prognostic importance in acute nephritis, chronic nephritis, nephrosis, nephrosclerosis, urologic conditions and heart failure. In extrarenal azotemia (hypochloremia and liver disease) the increase of the creatinine level is relatively less marked than that of urea and non-protein nitrogen apparently due to increased reabsorption of urea.

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HUNNER ULCER OF THE BLADDER (REVIEW OF 100 CASES) *

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IN 1836, Mercier [1] first mentioned ulcerations of the floor of the bladder causing perforation. Lawson Tait [2] in 1870 discussed a similar lesion and cited an additional case. Fenwick [3] in 1896 described in detail, "simple ulcer of the bladder," and mentioned the sudden onset of the disease characterized clinically by increased frequency of urination, dysuria, and intermittent hematuria.

As some confusion still exists as to the lesion which should be classified as a Hunner ulcer, it is of interest to refer to Hunner's original description in 1914.[4] He stated that the ulcer is found on the vertex, summit, or free portion of the bladder, in contrast to Fenwick's solitary ulcer which is observed on the base or fixed portion of the bladder. He further stated, "There is nothing absolutely characteristic in the cystoscopic picture. One's attention may be first arrested by slight, smooth, white scars of former ulceration rather than by the slight hyperemia or inflammatory spots near these scars." In other cases there is a small area of granulation which bleeds upon distention of the bladder or bleeds easily upon being touched. In certain instances, the same inflammatory spot is occupied and surrounded by an area of edema. Keene [5] in 1920 referred to this condition as circumscribed, panmural, ulcerative cystitis. Other authors have called it interstitial cystitis, elusive ulcer, panmural cystitis, submucous fibrosis, and submucous ulcer. In 1930, Bumpus [6] used the term, "interstitial cystitis," and stated, "As knowledge of the disease has grown, it has become apparent that the areas are frequently very extensive and not localized to any one portion of the wall of the bladder."

There is but little doubt that earlier urologists probably overlooked the so-called "Hunner ulcer" because they failed to overdistend the bladder. The condition, therefore, frequently was designated as "cystic neuralgia or neurotic bladder," and since it was overlooked so frequently the term "elusive ulcer" was ascribed to it. Hinman,[8] in 1939 favored calling this ulcer of the bladder a Hunner ulcer. In recent years, Kretschmer,[9] Folsom,[10] Peterson and Hager,[11] Young,[12] Quinby,[13] and others have published reports describing this lesion with its clinical manifestations.

ETIOLOGY

Hunner [4] observed the probable relationship between focal infection and Hunner ulcer of the bladder, the sites from which the infection was dis-

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seminated being the teeth, tonsils and sinuses, the infection being carried to the bladder by the blood stream.

Meisser and Bumpus,[14] in 1921, stated, "if it is assumed that such cases of cystitis are of focal origin, instead of being invariably the result of an adjacent infection, many aspects of the disease can be explained. Under certain conditions the infecting organism may cause generalized cystitis or, if the inflammation becomes localized in one area of the bladder, necrosis of the mucosa will result in a simple ulcer of the bladder. The organisms may lodge deeper in the wall of the bladder. In such an event the pathologic process will occur entirely below the mucosa and that rare type of ulcer first described by Hunner results."

Kretschmer [9] does not agree that Hunner ulcer occurs more frequently in women because of infection in the cervix and adnexa. In the 14 cases reported by Kretschmer, careful pelvic examinations were made but no pelvic pathology was found.

In a review of 110 cases, Hinman [8] made a careful search for foci of infection. Of six men with Hunner ulcer, three had a positive history of gonorrhea and one had syphilis with a primary genital chancre. The most significant fact in this review, however, was that of the women from whom a detailed past history was elicited, 80 per cent had had pelvic inflammatory disease, induced abortions, ectopic pregnancies or marked menstrual disorders. Keene,[15] in a report of the treatment of 25 cases, carefully eradicated all foci of infection, without procuring symptomatic relief in a single instance. In 1925, Peterson and Hager [11] questioned why organisms in foci common to both sexes should show a selective affinity for the bladder in women.

In our series, 58 per cent had demonstrable foci of infection in the teeth, tonsils, or cervix. Diseases of the upper urinary tract, such as pyelonephritis, hydronephrosis, or infected hydronephrosis, were present in 19 per cent. Three of the men had coexisting chronic prostatitis, and one had syphilis. Allergy was present in 19 per cent of the patients.

Incidence

Hunner ulcer of the bladder is preponderantly a disease of women. Hunner especially emphasized the prevalence of the disease in the female sex. All of his series of 25 cases were in women. In Hinman's series of 110 cases, only six were observed in men. In 1931 Folsom [7] cited a series of 20 cases of Hunner ulcer, of which 17 occurred in women and three in men. Kretschmer,[9] in 1922, in his series of 14 cases, noted that the ulcer occurred in 13 instances in women. Of 15 cases of Hunner ulcer reviewed by Bumpus,[6] 13 were in women. Peterson and Hager,[11] in 1707 urologic patients consisting of 1292 men and 415 women, reported the occurrence of Hunner ulcer in eight women.

In our group of 100 cases of Hunner ulcer, 94 occurred in women and six in men. The youngest patient was 18 years of age, and the oldest 77 years. The average age was 48 and a half years. All were in the sixth decade of life but two, who were 21 and 28 years of age respectively.

Pathology

The pathology in Hunner ulcer consists essentially of submucous inflammation of the bladder wall. Cellular infiltration occurs and, according to Peterson and Hager, nothing in the microscopic picture of the lesion is pathognomonic of the disease.

Young [12] states that the predominant pathological process is found in the deeper layers of the bladder wall. A portion of the loose areolar tissue of the submucosa has been replaced by fibrosis and the lesion may be very small. In instances where the lesion is circumscribed and confined to a small area of the bladder, the bladder wall itself shows little or no increase in thickness at the point of involvement. However, in other cases in which the inflammatory process has extended through all layers of the bladder wall and has involved the muscularis layer, considerable thickening of the bladder wall in the involved area may be observed. The mucous membrane overlying these lesions may be intact and may reveal edema or congestion. In other instances, linear ulcerations or small areas of scarring may be observed. From such a pathological process the mucous membrane becomes attached to the inelastic and dense underlying fibrotic area and causes tearing and bleeding of the mucous membrane when the bladder is overdistended.

The microscopic pathology is very similar to that of chronic cystitis except for the fibrosis in the submucosa. Varying degrees of round-cell infiltration are present beneath the fibrous lamella, and often between the muscle bundles as far as the serous layer. There may be increased vascularity with numerous newly formed capillaries in the submucosal layer. The characteristic pathologic lesion of the disease stated by Young, however, is a dense fibrosis which may involve the submucosa to varying degrees or, when more pronounced, may involve the muscularis layer.

Symptoms

The subjective manifestations of Hunner ulcer are characteristic. A constant symptom is diurnal and nocturnal frequency. The term, "clock-like" frequency of urination, has been suggested by Furniss.[16] Bumpus [6] states that freedom from symptoms at night indicates that the disease is not a Hunner ulcer. The marked frequency and clock-like character are produced by the inflammation of the bladder wall which acts as a splint, thereby causing considerable pain upon overdistention. The next most constant symptom is definite suprapubic pain which is aggravated by jarring or overdistention of the bladder or by voiding.

This entity probably is overlooked frequently because widespread destructive processes can occur in the bladder without giving rise to proportional objective urinary findings. Hematuria is not an unusual finding, and was noted prior to treatment in 18 per cent of this series. Hinman reports similar observations in 110 cases. He states that the initial examination of the urine was negative for pus, blood or organisms in 22 instances and positive for one or more in 70.

In this series, red blood cells were observed in the urine in 58.1 per cent of the cases and pus cells in 61 per cent. Undoubtedly, the frequent and prolonged local treatment to the bladder before these patients entered the clinic for cystoscopic study accounts for such a high percentage of patients with pus in the urine. In 11 patients in this series there was premenstrual aggravation of the bladder symptoms. Other urinary symptoms such as urgency, tenesmus, burning, tenderness, and backache were not as frequent as the symptoms previously mentioned.

Diagnosis

The diagnosis of Hunner ulcer is established by presumptive evidence in the history and cystoscopic visualization of the lesion.

Occasionally, because of the pronounced reduction in the bladder capacity which may not exceed 60 to 90 c.c. of solution, the ulcer cannot be recognized. However, if spinal anesthesia is administered, the ulcer usually can be seen. The cystoscopic picture is variable and, to a large extent, depends upon the degree of healing present. In some instances, the lesion on the bladder wall looks like a crushed strawberry. In cases in which the ulcer is healed, a small white area which cracks and bleeds when the bladder is overdistended exposes the site of the lesion.

Usually the ulcer is located upon the apex or dome or the free portions of the bladder, and may be single or multiple. In our series, a single lesion was present in 71 instances, and multiple ulcers were observed in 29.

In patients with Hunner ulcer who complain of supra-pubic pain, the pain may be reproduced during cystoscopy by touching the ulcer with the tip of the ureteral catheter.

Differential Diagnosis

The differential diagnosis usually is not difficult to make if characteristics of the lesion are kept in mind. Hunner ulcer may be confused with simple ulceration or an ulceration of tuberculous origin. Several characteristics, however, make possible an accurate diagnosis, namely, (1) the location of the ulcer on the apex, dome, or free portion of the bladder, (2) the absence of the excavation of a true ulcer, unless the lesion has been previously fulgurated, (3) the presence in tuberculous ulcer of renal tuberculosis or the finding of the tubercle bacilli in the urine by culture or by guinea pig inoculation.

As a rule, the surface of a Hunner ulcer is not covered with a deposit of salts as may be observed in incrusted cystitis, malignancy, and simple ulcer. Syphilis, although rare in any case as a cause of bladder ulcer, may be ruled out by complement fixation tests.

Acute cystitis is differentiated by the history, pyuria, and cystoscopic study. In extravesical lesions such as salpingitis, diverticulitis of the colon, or malignant growths, which adhere to the bladder wall and produce marked urinary symptoms, cystoscopic study reveals an area of inflammation on the bladder wall surrounded by bulbous edema. However, such a lesion does not closely simulate a Hunner ulcer and complete examination reveals the causative factor. Ulceration of the bladder following the application of radium to the cervix or vagina may produce symptoms resembling those of Hunner ulcer of the bladder. The patient may seek consultation years after the radium has been applied and cystoscopic study reveals ulcerations upon the base or the trigone of the bladder. In this group, the location of the ulcer and a history of previous radium therapy establishes the diagnosis. Careful inspection of the bladder and mild overdistention aid in establishing an accurate diagnosis of Hunner ulcer. As has been aptly stated, the lesion may be masked by prolonged medical treatment, or overlooked because of a coexisting cystitis.

Treatment

The treatment of Hunner ulcer of the bladder constitutes one of the most difficult procedures in urology. The ineffectiveness of any one type of treatment is attested by the numerous procedures being employed at the present time.

In his original communication, Hunner advocated the radical excision of the ulcer-bearing area of the bladder. Later, however, he advocated more conservative procedures and recommended electrocoagulation which produced startling results if only one area was involved in the bladder. As a rule, however, the relief of symptoms lasted only from six months to one year, and a second treatment was required.

Considerable care must be exercised in overdistending the bladder as rupture at the site of the ulcer may occur. Similarly, by repeated electrocoagulation of the lesion, the blood supply to the area may be impaired and subsequent treatment may cause slough and gangrene of the bladder wall. Both complications have been reported in the literature.

Bumpus [6] reported a series of more than 100 cases treated only by distention of the bladder with fair results in every case but one. Peterson and Hager [11] consider conservative treatment to be the method of choice; namely, transurethral electrocoagulation, overdistention of the bladder or a combination of the two procedures. It has been stated that the results from overdistention of the bladder have been as satisfactory as those secured by fulguration of the ulcer. The question is raised as to whether or not the

increased scar formation following fulguration would be of any final benefit.

In one case Quinby [13] resected the presacral nerve and obtained definite relief of pain without affecting the ability of the bladder to hold urine.

Howard [17] has suggested the use of emetine hydrochloride. Hinman [8] used this drug in three cases and stated that one patient was benefited. In six of our cases in which the drug was prescribed marked alleviation of symptoms occurred in two instances.

At the present time, the consensus of opinion is that many patients will be relieved by fulguration and by hydrostatic pressure. A few will be cured completely, but the treatment may have to be continued at varying intervals of time for years.

For complete relief in a small group of well selected cases in which the bladder capacity is reduced to practically nil, transplantation of the ureters into the bowel may be advocated.

Folsom [10] recommends subtotal resection of the bladder in patients with advanced Hunner ulcer and reports a series of experimental observations of regeneration of the bladder in dogs. This operation has been performed in eight patients. All have been relieved of their bladder distress, one case for 17 years, one for three years, and the remainder for from a few months to two years.

He concludes, " We feel that subtotal cystectomy is a safe surgical procedure; that any very serious infection of the upper urinary tract is a definite contraindication; that it will completely relieve the patient of the intolerable bladder irritation and pain; that success will depend on a complete removal of all the mobile parts of the bladder; that a new functionally satisfactory bladder will be regenerated; that a certain number of patients so operated will have some degree of regurgitation to the upper urinary tract; that the fact of good functional and anatomical regeneration after subtotal cystectomy will encourage us to a wider use of this procedure in other serious lesions of the bladder, as in carcinoma."

Treatment and Results

In our series of cases many different types of treatment were employed. In all cases a diligent search for foci of infection was instituted and such foci eradicated if present.

In 69 patients fulguration combined with overdistention and irrigations of the bladder was employed. In 49 cases the sharp pointed electrode was used, in 16 the ball electrode, and in four the type of electrode was not stated. This treatment was preceded by one or more irrigations of the bladder to ascertain whether or not they would be of value in the individual case. In the majority of instances fulguration of the ulcer and overdistention of the bladder were performed under either nitrous oxide or spinal anesthesia.

Of this group, 17 were definitely cured; 10 were lost trace of in the follow-up period; and 14 were not improved. Three partial resections of the ulcer-bearing area of the bladder were performed later. One patient in whom this was done was greatly improved. The last patient had a recurrence of symptoms and, as a last resort, the ureters were transplanted into the bowel with a resultant cure.

In one case in this group, resection of the presacral nerve was done without relief of symptoms. Twenty-eight patients were improved, many having periods of freedom from distress for months after fulguration and overdistention. With recurrence of symptoms, relief again was afforded by repeated fulguration and overdistention. Nine patients were treated by irrigations and overdistention; two were cured; there was no follow-up in five; one was improved; and one became worse.

Three patients were treated by irrigation and instillation of 4 per cent argyrol at the time of the initial examination, but they failed to return for further treatment. One patient was given irrigations and instillations of 16 per cent gomenol with marked alleviation of symptoms.

Three patients had fulguration alone with moderate relief of symptoms. Two of the male patients were completely cured by eradication of the chronic prostatitis, one by prostatic massage and the other, having coexisting prostatic hypertrophy, by prostatectomy.

Ultraviolet irradiation was applied directly to the ulcer by means of a quartz tube conductor in two cases, with questionable improvement in symptoms.

Bilateral transplantation of the ureters was performed in four additional cases. One patient died of pneumonia 10 days after operation, and the remaining three patients were completely relieved of symptoms.

Five patients did not return for treatment after the diagnosis had been established and were referred to their family physician for treatment.

Two patients have received treatment too recently to be mentioned in the series.

Conclusions

Hunner ulcer is predominately a disease of women, although it may be observed in men.

In this series, it was a disease of middle life, the greater percentage of our cases occurring in the fifth decade.

Foci of infection should be eradicated in all cases.

The symptom complex of Hunner ulcer is diurnal and nocturnal frequency with associated dysuria and suprapubic pain. This group of symptoms was present in over 90 per cent of the patients in our series. The average bladder capacity in this series was 135 to 140 c.c., which indicates a decidedly diminished capacity.

The treatment of choice in our series, as indicated by the results, is conservative treatment, followed by radical treatment only if this fails to afford relief.

Fulguration of the ulcer with the electrode combined with overdistention of the bladder under anesthesia is the procedure of choice in our series.

Transplantation of the ureters into the bowel should be employed only if all other conservative measures have failed to give relief.

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A ROENTGEN STUDY OF CAVITIES IN PULMONARY TUBERCULOSIS; CAVITY CHANGES UNDER COLLAPSE AND NON-COLLAPSE MEASURES *

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Frequently, the clinician's estimate of results over a period of years is at wide variance with actual results as tabulated by a definite statistical study of the same material. While mathematical calculations can never be applied specifically to any individual case in medicine, nevertheless, results of the past should be used as a rough guide in determining relative values for present decisions and prognostications. In an effort to aid in the evaluation of therapeutic results in cavernous tuberculosis, a study based on the interpretation of chest roentgenograms was initiated. The paper has been limited primarily to individual cavity changes and, therefore, cavity closure does not necessarily infer controlled tuberculosis.

Hospital records were examined of all patients admitted to Hopemont Sanitarium, Hopemont, West Virginia, from July 1925 to July 1938. No observations were extended beyond July 1939. A period of observation for at least one year after admission was thereby obtained.

Within limits, this is a study of selected cases and selected cavities. Only proved cases of tuberculosis with adequate roentgen studies and with at least six months of controlled therapy were used. All cases leaving the sanatorium or cases in which death occurred prior to the six month period were excluded. Only cavities with a complete roentgen outline were used. Although many early cavities, especially in the presence of exudative disease, did not show definite cavity walls most of these on later films became definite, showed complete cavity walls and were then included in the series.

The total number of usable cases was 750 and the total number of usable cavities in these cases was 1097.

Classification of cases with reference to sex and average age was made. There were 439 females and 311 males. The ratio of females to males was 59–41. The general admissions to Hopemont for the same year period show a ratio of 62–38. The average age for the females was 26, for the males 29, and the combined average age was 27. In both male and female the greater incidence of disease in the third and fourth decade is emphasized.

Classification of cases with respect to extent of disease has been made using the National Tuberculosis Association Classification as a standard. Discrepancies in comparing results in tuberculosis therapy, not only in dif-

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ferent institutions but also in the same institutions for different year periods, have been due largely to the wide variation of cases that may come under the classification of far advanced disease. Recognition of this fact has led the staff at Hopemont to adopt a modified classification.[1] Under this grouping the National Tuberculosis Association Classification is applied separately to each side in addition to its usual application to the case as a whole. If there is sufficient disease on one side alone to make the case moderately advanced then that side is classified as moderate. Under the Standard Classification only 5 per cent of the cases in the study are moderately advanced whereas 95 per cent are far advanced. Under the Modified Classification it is further noted that 78 per cent of the cases fall into either the far and moderate or far and far advanced groups.

It is readily admitted that should an equal number of cases be studied composed of 95 per cent far advanced disease the results of similar therapy should not vary greatly. However, if in the one instance a high percentage of the far advanced cases is made up of moderate and moderate, far and clear, and far and minimal cases, and in the other instance a high percentage of the far advanced cases is made up of far and moderate, and far and far cases then the results would actually show wide variations.

Individual cavities have been measured in centimeters at the widest diameter on the 72 inch postero-anterior film and have been divided into the following five groups: 0–2 cm., 2–4 cm., 4–6 cm., 6–8 cm., 8 plus cm. In instances of multiple cavitation where it was impossible to follow individual cavities on consecutive films, the total diameter of the multiple cavitation was taken and considered as a single cavity. Cavities measuring exactly 2, 4, 6, or 8 cm. were alternately placed in the higher and lower divisions.

Therapeutic Measures

Roentgen changes in individual cavities were tabulated for patients on bed rest, mild activity, phrenic nerve surgery, pneumothorax, and thoracoplasty. By bed rest is meant absolute rest in bed for the entire 24 hours daily. Mild activity varies from one bathroom privilege daily to two hours exercise plus bathroom and dining room privileges. Phrenic nerve surgery includes permanent, temporary, and repeat procedures. By pneumothorax is meant intrapleural pneumothorax. Cavity changes were credited to pneumothorax even in the presence of pneumonolysis or combined phrenic surgery and pneumothorax procedures. Cavities were considered to be under pneumothorax until complete reëxpansion of the lung was seen by roentgenogram. Thoracoplasty includes all cases in which ribs were removed for the purpose of obtaining collapse of the lung. Phrenic nerve surgery, pneumothorax and thoracoplasty actually consist of these procedures plus bed rest. Cavities were considered closed only when roentgen studies failed to reveal any evidence of open cavity. Blocked cavities occurred in 15 of the 750 cases, a 2 per cent case incidence. These cavities were considered

closed only when they were replaced by a dense homogeneous shadow which persisted throughout the remainder of the study. Only cavities that had a minimum of six months on any given therapy have been listed under that therapy. The same cavity if observed for six or more months under more than one procedure has been listed under each procedure. Thus, while the cavities present in this series total 1097, the therapeutic results for these cavities total 1333.

Results of Therapeutic Measures

Results short of complete cavity closure are not satisfactory and yet it is of interest to determine changes in size under each procedure. A tabulation of all cavities showed 35 per cent of the cavities closing, 20 per cent becoming smaller, 17 per cent remaining the same and 28 per cent becoming larger. Cavities were closed or made smaller more frequently by collapse measures than by non-collapse measures (chart 2, graph 1).

In bilateral cavitation cases where collapse measures had successfully controlled one side, there were 29 open cavities on the opposite side. The following results were obtained on these 29 cavities under the various forms of therapy:

	Open	Closed
Bed rest	5	8
Mild activity	1	1
Phrenic surgery	1	1
Pneumothorax	0	12
Total	7	22

In the collapse therapy series combined collapse measures were used for 136 cavities and pneumonolysis was a factor in 32 cavities under pneumothorax. Phrenic nerve surgery, pneumothorax, and thoracoplasty were used for seven cavities, phrenic nerve surgery and thoracoplasty for eight cavities, and pneumothorax and thoracoplasty for one cavity. All of these 16 cavities were closed by thoracoplasty. There were 120 cavities treated by phrenic nerve surgery and pneumothorax. Of this number 24 remained open and 96 were closed. Under pneumothorax plus pneumonolysis three cavities remained open and 29 were closed.

Chart I

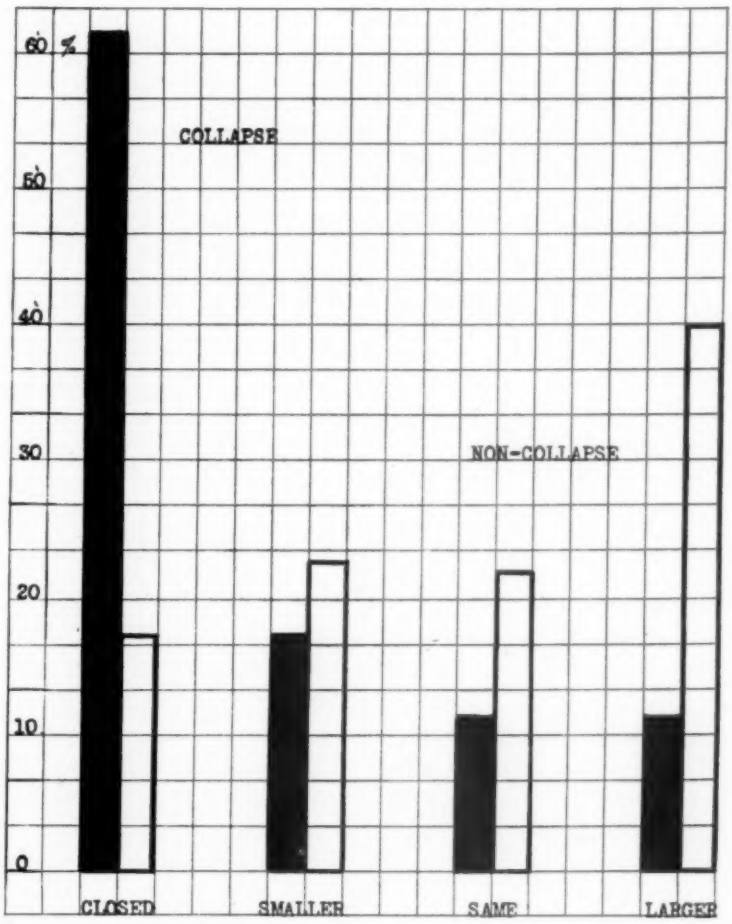
Distribution of Cavities

Therapy	0–2 cm.	2–4 cm.	4–6 cm.	6–8 cm.	8 plus cm.	Total
Bed rest	28	128	130	78	165	529
Mild activity	13	78	71	49	53	264
Phrenic surgery	3	33	48	29	56	169
Pneumothorax	11	70	140	45	75	341
Thoracoplasty	0	1	10	5	14	30
Non-collapse	41	206	201	127	218	793
Collapse	14	104	198	79	145	540
Total	55	310	399	206	363	1333

CHART II

Therapy Results in Unclosed Cavities

Cavity Size	Smaller			Same			Larger		
	Non Coll.	Coll.	Total	Non Coll.	Coll.	Total	Non Coll.	Coll.	Total
0–2 cm.	1	1	2	4	0	4	19	1	20
2–4 cm.	41	12	53	30	10	40	73	7	80
4–6 cm.	40	18	58	42	14	56	86	17	103
6–8 cm.	33	20	53	23	10	33	53	12	65
8 plus cm.	58	39	97	72	27	99	81	22	103
Total	173	90	263	171	61	232	312	59	371
Per cent	22	17	20	21	11	17	40	11	28



GRAPH 1. Cavity results—collapse versus non-collapse in 1333 cavities.

Cavity Closure

A study of the cavities closed under therapy calls attention to a number of important considerations. There were 529 cavities on bed rest, 264 on mild activity, 169 on phrenic nerve surgery, 341 on pneumothorax, and 30 on thoracoplasty. Cavity closure occurred more frequently in the smaller cavities under every mode of therapy. The percentage of closed cavities under bed rest therapy is 13 and that obtained under mild activity is 25. The greater preponderance of exudative disease and the larger total cavitation present in the cases on bed rest are in great part responsible for this discrepancy. Phrenic nerve surgery resulted in 24 per cent cavity closure, pneumothorax 76 per cent, and thoracoplasty 93 per cent. The unusual results of thoracoplasty are due to conservative selection of cases for this procedure. Since, however, the total number of thoracoplasty cases included is but 30 in a series of 1333 therapeutic results their influence on percentage is slight.

CHART III

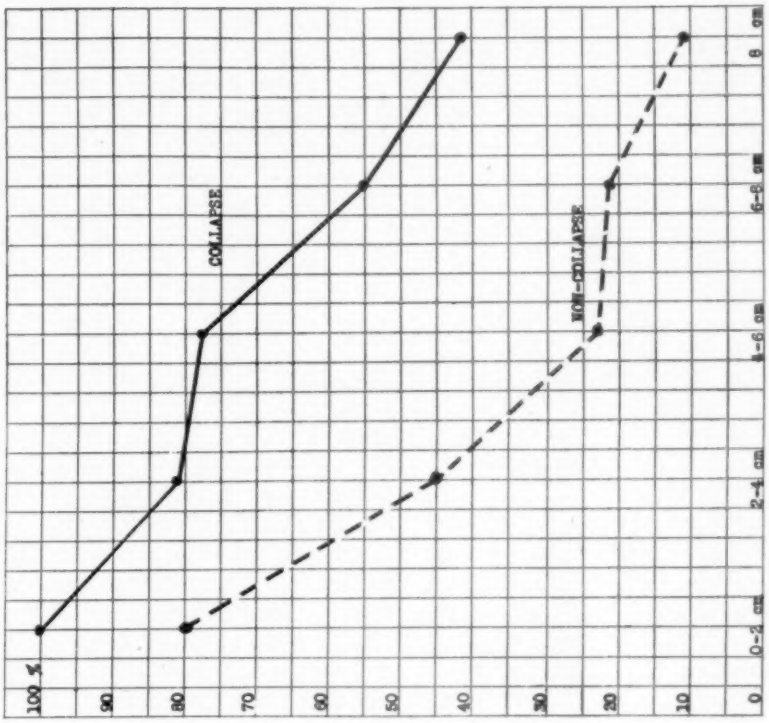
Cavity Closure

A Study of 1097 Cavities with 1333 Therapy Results

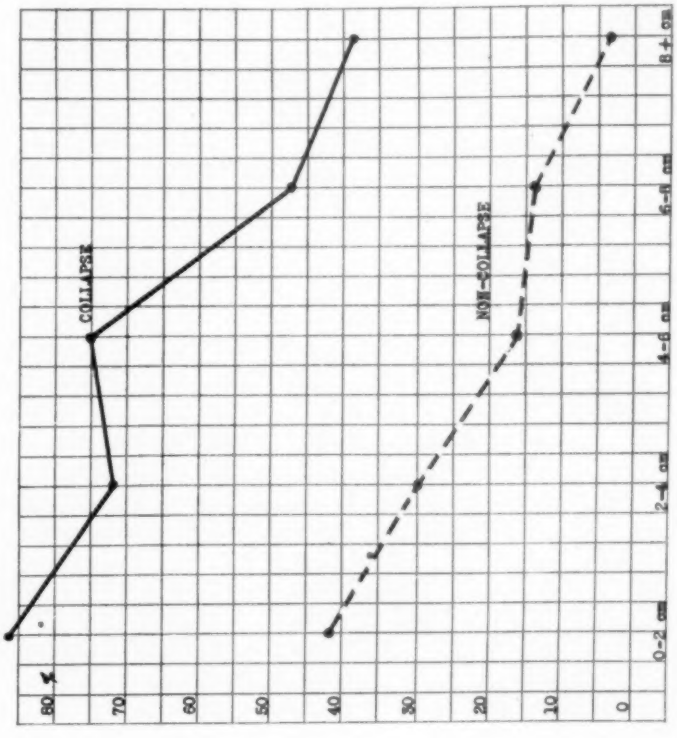
Therapy	0–2 cm.		2–4 cm.		4–6 cm.		6–8 cm.		8 plus cm.		Total	
	No. Closed	% Closed	No. Closed	% Closed	No. Closed	% Closed	No. Closed	% Closed	No. Closed	% Closed	No. Closed	% Closed
Bed rest	8	28	33	26	17	13	10	13	3	2	71	13
Mild activity	9	69	29	37	16	22	8	16	4	8	66	25
Phrenic surgery	2	66	13	39	20	42	3	10	4	7	42	24
Pneumothorax	10	91	61	87	119	85	30	67	40	53	260	76
Thoracoplasty	0	0	1	100	10	100	4	80	13	93	28	93
Non-collapse	17	42	62	30	33	17	18	14	7	3	137	17
Collapse	12	86	75	72	149	75	37	47	57	39	330	61
Total	29	53	137	44	182	45	55	21	64	17	467	35

If the 793 cavities on bed rest and mild activity are compared with the 540 cavities on phrenic surgery, pneumothorax, and thoracoplasty, it will be noted that in the non-collapse series closure occurred in 137 cavities, a total of 17 per cent. In the collapse series closure occurred in 330 cavities, a total of 61 per cent. Furthermore, in the non-collapse group the percentage of closures ranges from 42 per cent in the 0–2 cm. cavities to 3 per cent in the cavities over 8 cm. The collapse group ranges from 86 per cent to 39 per cent for similar diameters (chart 3, graph 2).

It seems logical to assume that a cavity which represents the total pulmonary cavitation will close more readily than a similar cavity which represents only a part of the total cavitation; therefore a separate study of the 457 cases with single cavitation was also made. There were 573 therapeutic



GRAPH 3. Cavity closure in 573. Single cavitation cases.



GRAPH 2. Cavity closure—collapse versus non-collapse in 1333 cavities.

results in this series. Closure was accomplished in 65 of the 245 cavities under non-collapse measures, or 26 per cent, and in 216 of the 328 cavities under collapse measures, or 65 per cent. In comparing the single cavity series with the complete series, it is noted that, since the non-collapse closures were raised from 17 per cent to 26 per cent and the collapse closures from 61 per cent to 65 per cent, the presence of single cavitation more definitely improved the results in the non-collapse group. The same trend was noted in the subdivisions based on cavity diameter (chart 4, graph 3).

CHART IV

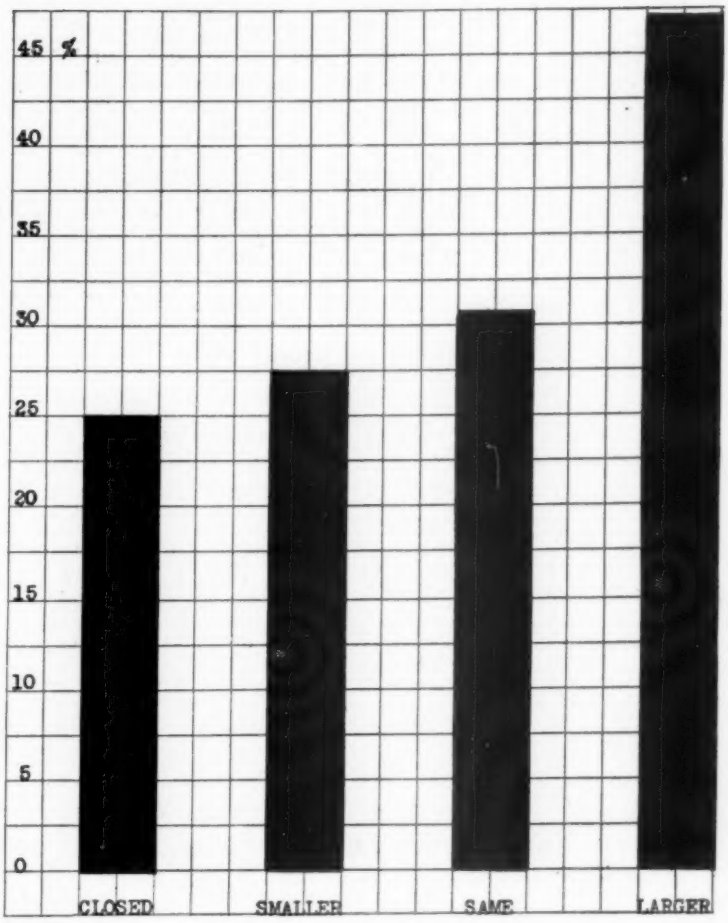
Cavity Closure

A Study of 457 Single Cavity Cases with 573 Therapy Results

Therapy	0–2 cm.		2–4 cm.		4–6 cm.		6–8 cm.		8 plus cm.		Total	
	No. Closed	% Closed	No. Closed	% Closed	No. Closed	% Closed	No. Closed	% Closed	No. Closed	% Closed	No. Closed	% Closed
Bed rest	0	0	13	46	6	18	2	10	3	8	24	20
Mild activity	4	100	15	44	11	26	8	30	3	15	41	32
Phrenic surgery	1	100	7	53	14	40	3	15	2	5	27	26
Pneumothorax	4	100	27	93	90	89	21	80	21	58	163	83
Thoracoplasty	0	0	1	100	9	100	4	80	12	92	26	93
Non-collapse	4	80	28	45	17	23	10	22	6	11	65	26
Collapse	5	100	35	82	113	78	28	50	35	42	216	65
Total	9	90	63	60	130	59	38	39	41	29	281	49

COMPARISON OF CAVITIES IN THE COLLAPSE AND NON-COLLAPSE GROUPS

Before logical comparisons can be made between various forms of therapy the presence of definitely similar factors must be established. The incidence of exudative disease, the average total pulmonary cavitation present, the average number of months necessary for cavity closure, the average duration of each form of therapy, and the average period of observation after cavity closure are all considerations in a study of this type which can influence the results obtained. In evaluating these factors it is noted that in the non-collapse series 34 per cent of the cavities were present in cases showing a predominance of exudative disease to 32 per cent in the collapse series. The average total pulmonary cavitation present in the non-collapse group was 11 cm. whereas in the collapse group it was 8 cm. The average number of months required for closure in the non-collapse cavities was 16 and in the cavities under collapse it was 8. Both the non-collapse and the collapse series averaged 24 months on individual therapy measures. The non-collapse series was observed for an average of 24 months after closure and the collapse series for a 21 month average (charts 5 to 10).



GRAPH 4. Cavity results in the presence of predominantly exudative disease (see chart 6).

CHART V

Incidence of Predominantly Exudative Disease in Cavity Series

Therapy	0–2 cm.		2–4 cm.		4–6 cm.		6–8 cm.		8 plus cm.		Total	
	No. Exudative	% Exudative	No. Exudative	% Exudative	No. Exudative	% Exudative	No. Exudative	% Exudative	No. Exudative	% Exudative	No. Exudative	% Exudative
Bed rest	9	32	42	32	47	36	30	38	84	51	212	40
Mild activity	1	7	18	22	7	9	8	16	22	41	56	21
Phrenic surgery	1	33	3	9	9	18	9	31	24	43	46	27
Pneumothorax	4	36	22	31	41	29	16	35	33	44	116	34
Thoracoplasty	0	0	0	0	1	10	1	20	6	43	8	26
Non-collapse	10	25	60	29	54	26	38	30	106	51	268	34
Collapse	5	36	25	25	51	26	26	33	63	44	170	32
Total	15	27	85	27	105	26	64	30	169	46	438	33

CHART VI

Therapy Results in the Presence of Predominantly Exudative Disease

Cavity Size	Closed		Smaller		Same		Larger	
	No. Exudative	% Exudative	No. Exudative	% Exudative	No. Exudative	% Exudative	No. Exudative	% Exudative
0–2 cm.	6	20	0	0	1	25	8	40
2–4 cm.	28	20	11	21	10	25	36	45
4–6 cm.	44	24	14	24	9	16	38	36
6–8 cm.	14	25	11	21	7	21	32	49
8 plus cm.	22	34	37	38	46	46	64	62
Total	114	25	73	28	73	31	178	48

CHART VII

Average Diameter of Total Lung Cavitation in 1333 Individual Cavities

Therapy	0–2 cm.	2–4 cm.	4–6 cm.	6–8 cm.	8 plus cm.	Total
Bed rest	11 cm.	9	11	13	17	15
Mild activity	7	6	8	9	14	9
Phrenic surgery	6	6	7	9	12	8
Pneumothorax	6	7	7	9	14	9
Thoracoplasty		3	6	7	12	9
Non-collapse	10	8	10	12	16	11
Collapse	6	6	7	9	13	8
Total	9	8	8	11	15	11

CHART VIII

Average Months for Cavity Closure

Treatment	0–2 cm.	2–4 cm.	4–6 cm.	6–8 cm.	8 plus cm.	Total
Bed rest	14	14	20	21	11	16
Mild activity	16	15	14	19	64	18
Phrenic surgery	9	11	14	22	18	13
Pneumothorax	3	6	8	8	12	7
Non-collapse	15	15	17	20	42	17
Phrenic and pneumothorax	4	7	8.3	9	12.2	8

CHART IX

Average Months on Each Treatment

Treatment	0–2 cm.	2–4 cm.	4–6 cm.	6–8 cm.	8 plus cm.	Total
Bed rest	30	20	24	21	24	23
Mild activity	42	24	25	20	35	26
Phrenic surgery	17	21	21	18	22	21
Pneumothorax	23	24	27	27	26	26
Non-collapse	34	21	25	20.4	26	24
Phrenic and pneumothorax	22	23	26	24	24	24

CHART X

Average Months Observed After Cavity Closure

Therapy	0–2 cm.	2–4 cm.	4–6 cm.	6–8 cm.	8 plus cm.	Total
Bed rest	17	25	25	17	30	23
Mild activity	38	22	17	25	41	29
Phrenic surgery	6	24	20	18	16	20
Pneumothorax	35	20	16	26	25	20
Thoracoplasty	—	47	31	12	25	26
Non-collapse	28	24	21	21	36	24
Collapse	30	21	18	24	25	21

There is a marked similarity in the two groups in regard to the proportion of cavities occurring in exudative cases, the average duration of forms of therapy, and the average period of observation after cavity closure. However, the average total pulmonary cavitation is somewhat greater in the non-collapse group, whereas the average number of months necessary for cavity closure is twice as long in the non-collapse series as in the collapse series. Nevertheless the relative similarity of the factors involved in the non-collapse and collapse groups lends added significance to the findings of 17 per cent cavity closure for non-collapse measures and 61 per cent closure for collapse therapy.

CASES WITH ALL CAVITIES CLOSED

Closure of all pulmonary cavities was obtained in 331 of the 750 cases used in this study. There were 457 cases with single cavitation and 293 cases presenting two or more cavities. Closure of all pulmonary cavities was obtained in 60 per cent of the single cavity cases and in 17 per cent of the multiple cavity cases. The total percentage of cases with all cavities closed was 44.

SUMMARY

A study of 750 cases of cavernous pulmonary tuberculosis with 1097 individual cavities has been presented. Classification of cases as to extent of disease showed that 95 per cent were far advanced. Roentgen changes in individual cavities were noted for patients on bed rest, mild activity, phrenic nerve surgery, pneumothorax, thoracoplasty, and on combinations of these measures. Comparisons were made not only for each form of therapy but also for cavities of definite size under these forms of therapy. The results of non-collapse and collapse measures were tabulated and studies made to show the similarity of the cavities listed under these two major forms of therapy. Finally, the cases with complete cavity closure were presented.

Conclusions

1. Successful therapeutic results are inversely proportional to the diameter of total pulmonary cavitation, the diameter of the individual cavity, and the preponderance of exudative disease.

2. Individual cavities close more readily in single cavity cases than in multiple cavity cases.

3. Collapse measures are three times as effective as non-collapse measures in closing individual cavities.

4. In single-cavity cases collapse measures are twice as effective as non-collapse measures in closing the cavity.

5. The average time required for cavity closure is half as long with collapse therapy as with non-collapse therapy.

6. Closure of all cavities occurs four times as frequently with localized cavitation as with disseminated cavitation.

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IDIOPATHIC CARDIAC ENLARGEMENT OCCURRING IN INFANTS AND CHILDREN *

By J. Marshall Neely, M.D., F.A.C.P., *Lincoln, Nebraska*

Congenital idiopathic cardiac hypertrophy is a term which has been used to designate cardiac enlargement occurring in infants and young children with no demonstrable etiology. As more attention is given to this group of cases it becomes apparent that those which are truly idiopathic constitute a small minority. S. Van Creveld [2] and others have shown that many cases of cardiac enlargement thought to be idiopathic are Von Gierke's disease, or "hepatomegalia glycogenica," in which there is glycogen infiltration of the heart, liver, and kidneys. Cardiac enlargement has also been shown to occur in the primary anemias of childhood, particularly in sickle cell anemia. According to Kugel and Stoloff [7] some have attempted to explain cardiac hypertrophy and dilatation on the basis of so-called status thymico-lymphaticus. Kugel [9] divides cardiac enlargement of infancy into eight main groups: congenital defects, infections, anemias of long standing, non-suppurative myocardial degeneration, metabolic disorders, hypertension, tumors, and finally the unclassified. Vitamin B_1 deficiency has recently [13] been shown to play an important rôle in the production of cardiac hypertrophy of adults and its importance in infants must be considered.

The material upon which this communication is based is supplied from the clinical records, roentgen-ray films, and autopsy material from three infants.

Case Reports

Case 1. A male infant 25 days of age was admitted to the hospital because of difficult feeding, crying, and cyanosis. At the time of birth nothing unusual was noted and symptoms developed about 10 days before admission to the hospital. Rapid respiration and cyanosis were observed the day of admission to the hospital. Examination disclosed fever, grunting respiration, restlessness, sunken fontanels, and circumoral cyanosis. Respirations were about 100 per minute and breath sounds were harsh, particularly over both bases. No dullness could be elicited in either lung field. There was clinical evidence of an enlarged heart both by percussion and roentgen study. The pulse rate was estimated at 290. A cardiac murmur was heard over the precordium. The liver edge was at the umbilicus and the extremities were not remarkable. The patient died quite suddenly on the fourth hospital day. During the hospital stay the temperature varied from 100 to 103° F.

Postmortem Findings: There was slight pleural effusion in the pleural cavity. Both lungs were voluminous and firm in consistency. The heart weighed 80 gm. and there were no congenital anomalies evident. There was enlargement of the liver and to a lesser extent the spleen. Microscopically there was some fragmentation of the muscle in the myocardium and small areas of degeneration. There was also a slight

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From the Department of Radiology, Lincoln General Hospital.

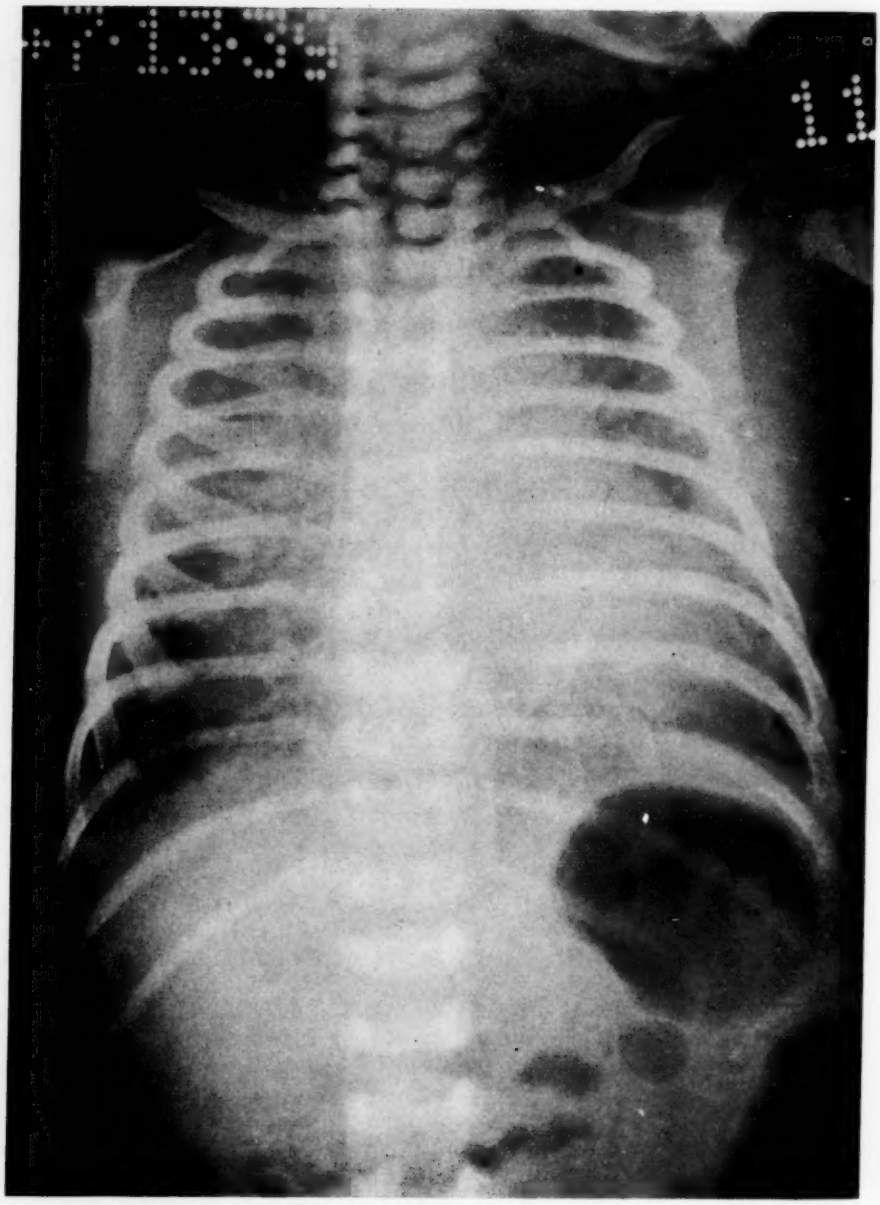

FIG. 1. A single A.P. film showing cardiac enlargement and decreased aeration throughout both lung fields. (Case 1.)

diffuse lymphocytic infiltration seen throughout the myocardium. Chronic passive congestion was present in the liver and kidneys. Sections of the lungs showed an advanced interstitial pneumonitis with thickening of the alveolar septae and lymphocytic infiltration. There was also evidence of collagen formation in the septae. Practically no capillaries could be found in the alveolar septa. The alveolar spaces were decreased in size or obliterated.

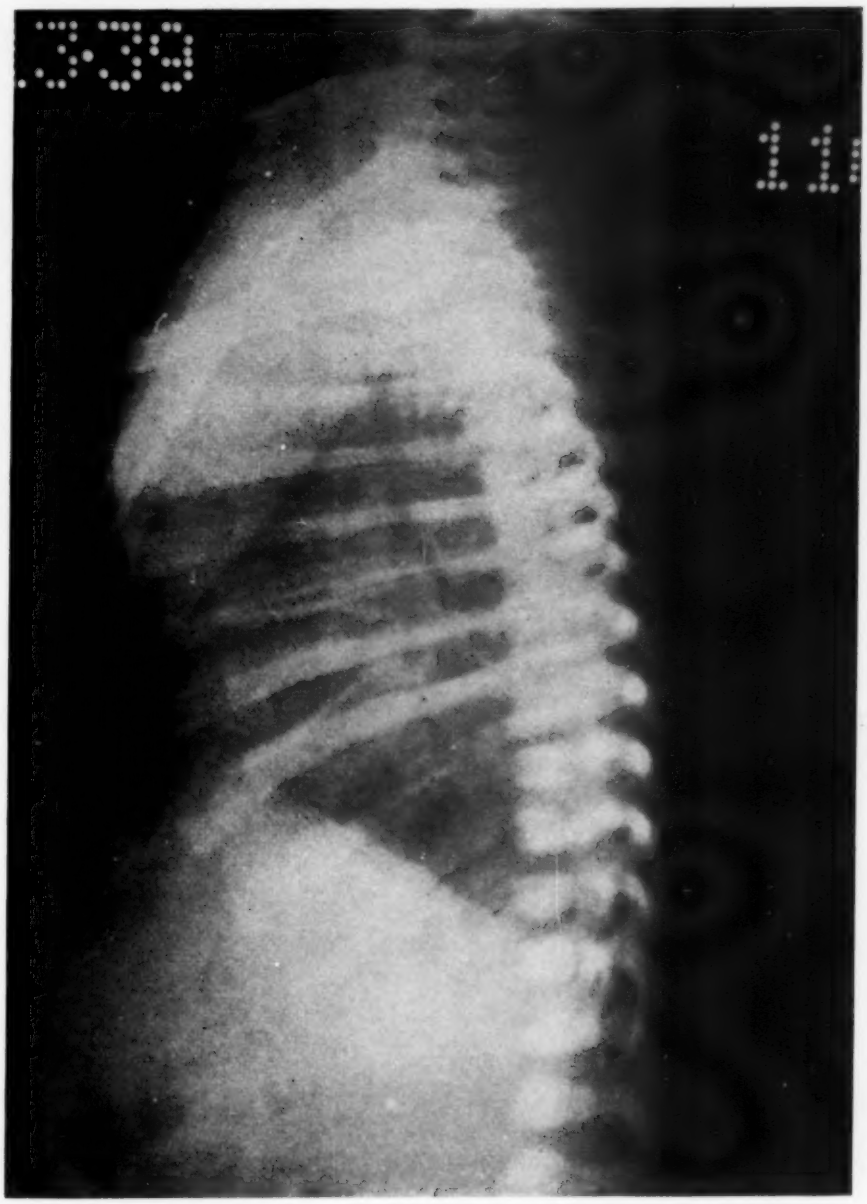

FIG. 2. In the lateral position there is no evidence of displacement of the trachea and the mottling is again seen in the lung fields.

Case 2. A white female infant, age 11 months, was perfectly well until the day of her death. No definite history of illness could be elicited from the parents. Death occurred quite suddenly while she was taking her bottle.

Postmortem Findings: There was marked cardiac enlargement without evidence of congenital defect. Hypertrophy was most pronounced in the right ventricle and there was dilatation of the right atrium. The left ventricle was about normal in size.

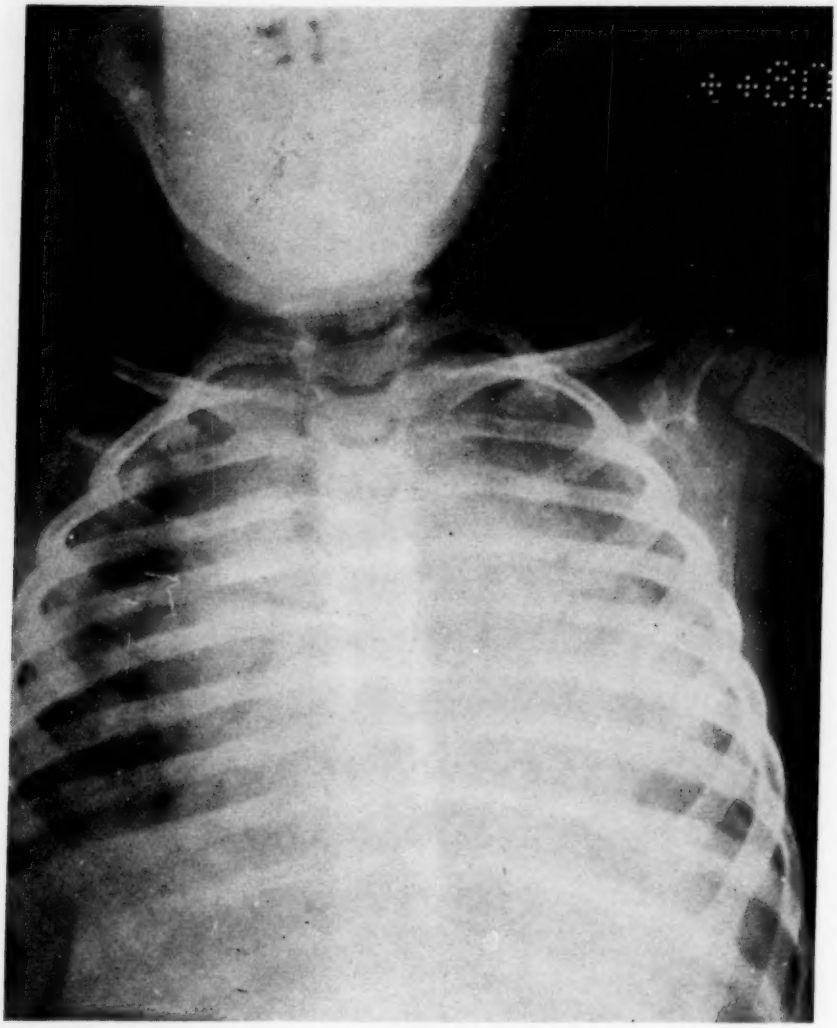

FIG. 3. A single A.P. film of the chest showing marked cardiac enlargement with some displacement of the trachea to the right. Configuration particularly suggests right heart enlargement. (Case 3.)

Both lungs were normal in size though there was less aeration than normal. The cut surfaces appeared somewhat meaty.

Microscopically the myocardium showed small areas of fragmentation and a slight polyblastic cellular infiltration. The lungs showed tremendous thickening of the alveolar walls with proliferation of alveolar phagocytes and, as demonstrated by means of Masson's trichrome stain, definite collagen formation. Very few capillaries were found. There were small areas of emphysema present.

Case 3. A white male child, age three years, was admitted to the hospital June 9, 1935, complaining of dyspnea, weakness, orthopnea and cough. Dyspnea was first noted about four weeks before admission and became much more noticeable about one week before admission. Associated with these symptoms was cough, non-productive

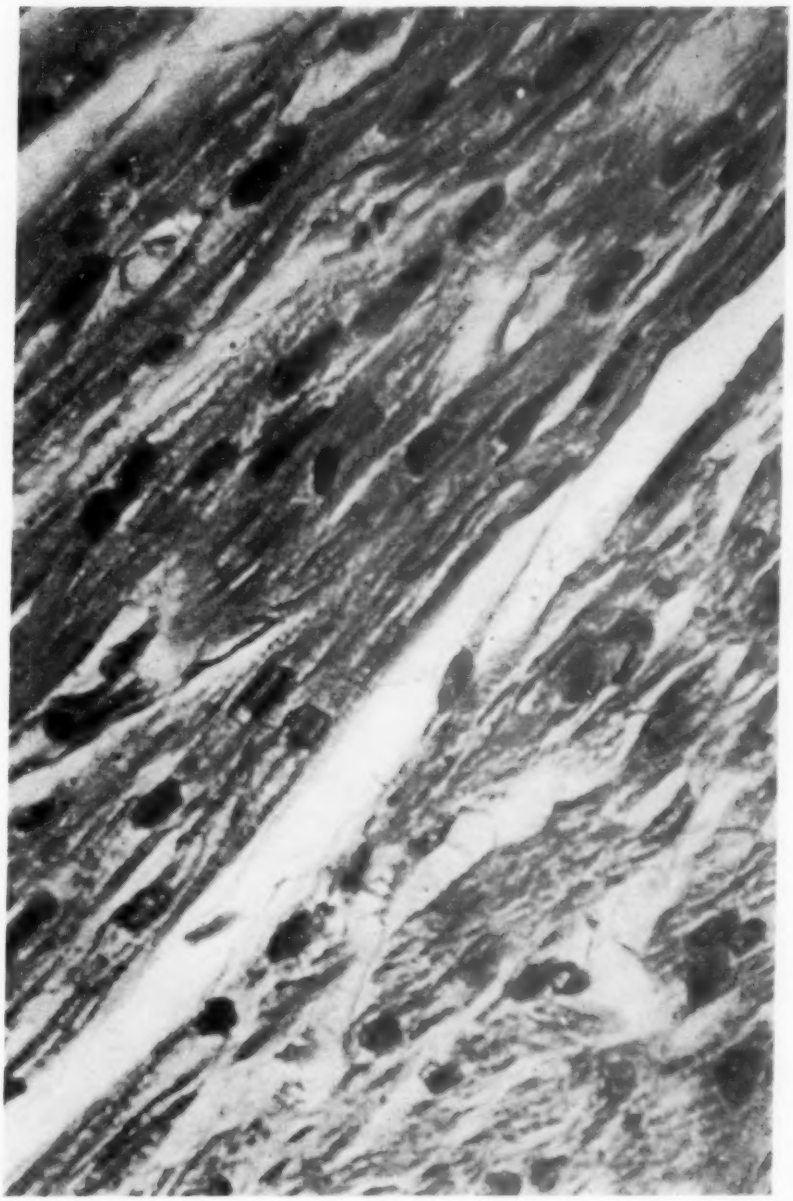

FIG. 4. Section of myocardium showing fragmentation of the muscle fibrils. Note mitotic figure near top of illustration.

in character, which became worse when the patient was lying down. Examination showed slight cyanosis, and labored rapid respiration. The left side of the chest was larger than the right. There were harsh breath sounds, and bronchial breathing could be heard below the left scapula. There was tremendous enlargement of the heart which was very rapid. No murmurs were heard. No fluid or masses could be found in the abdomen though there was enlargement of the liver and edema of the lower

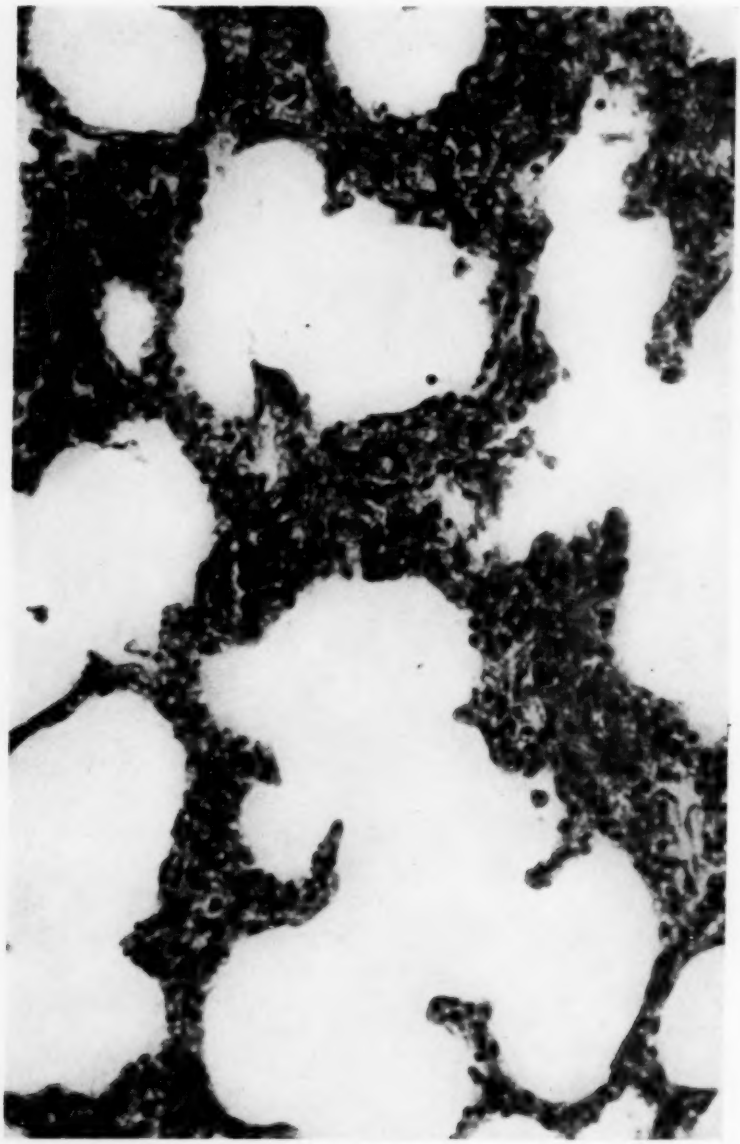

FIG. 5. Section of lung illustrating marked interstitial proliferation of alveolar septa with polyblastic cellular infiltration. Note absence of alveolar capillaries. (Case 1.)

extremities. A general anasarca developed terminally and death occurred on August 3, 1935.

Postmortem Findings: There was ascites and bilateral pleural effusion. The liver and spleen were enlarged due to passive congestion. The heart was markedly enlarged. There were no congenital anomalies present. There was marked right ventricular hypertrophy and the right atrium was so dilated that its wall was almost parchment thin. There was also dilatation of the pulmonary artery which measured

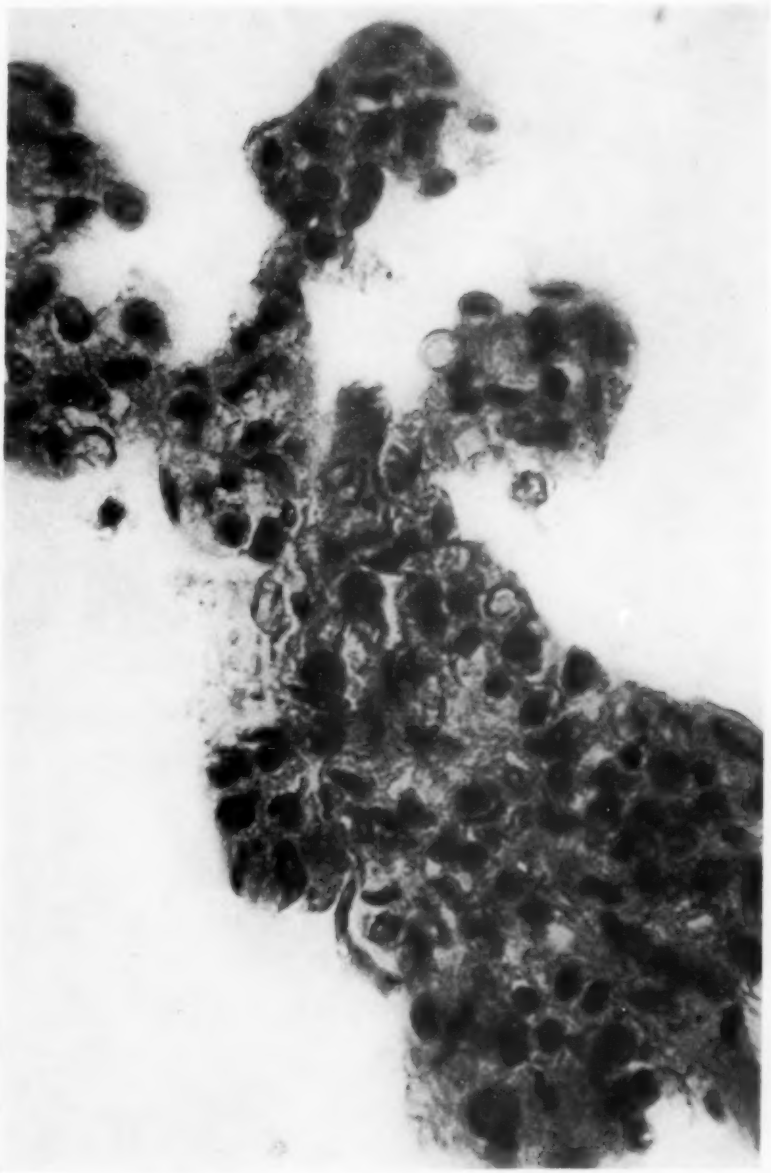

FIG. 6. Higher power view of same lung showing marked proliferation of histocytes and collagen formation. (Case 1.)

3 cm. at the base. Some small atheromatous plaques were seen in the intima of the pulmonary artery. The left lung was smaller than the right. Both were heavier than normal and small grayish areas were seen beneath the pleura. On cut section there was evidence of emphysema though the cut surface was quite firm in consistency. Microscopically many lung sections showed an advanced chronic pulmonary emphysema; in some areas a definite interstitial pneumonitis existed. The myocardium

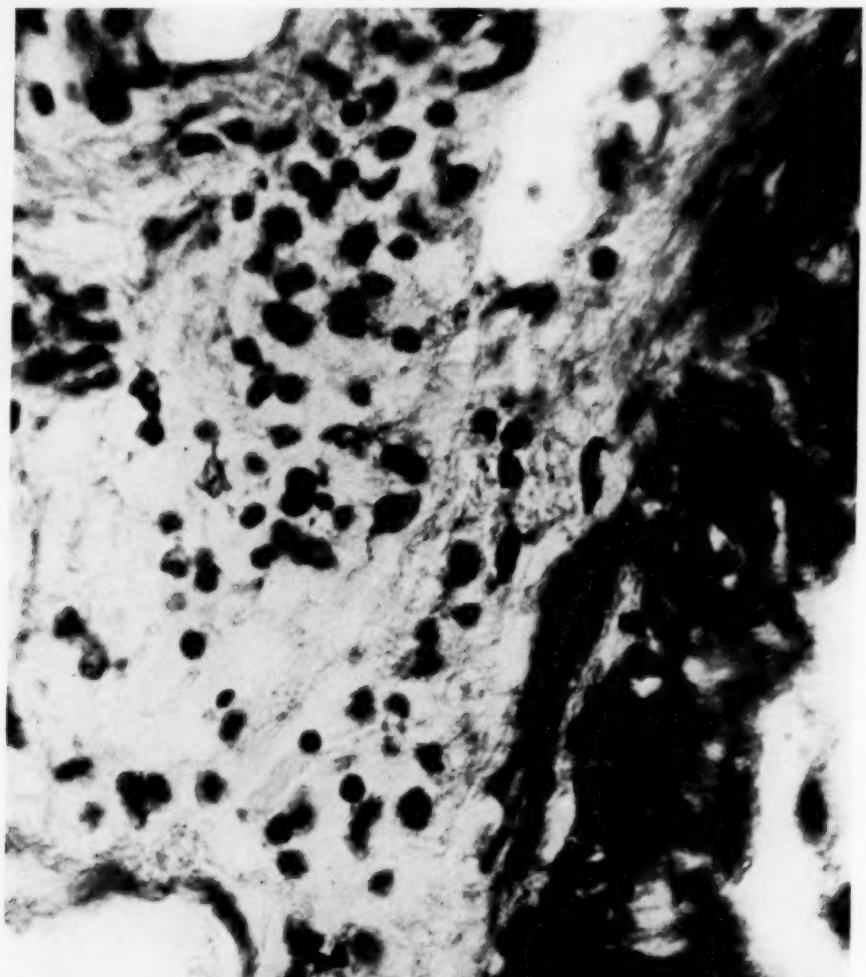

FIG. 7. Section of bronchial wall showing edema and cellular infiltration.

showed hypertrophy of the muscle fibers and very small patches of fibrosis. There was also marked passive congestion of the liver, kidneys, and spleen.

While these three clinical courses vary considerably there are certain symptoms and findings common to all. Dyspnea, cyanosis, rapid pulse and cardiac enlargement were present in each, though in the child who died

suddenly, cardiac enlargement was not discovered until after death. The length of illness varied from sudden death to three months. According to Mahon [5] the average age incidence in idiopathic cardiac hypertrophy is 14 months. The onset is usually rapid and the three cardinal findings are cyanosis, dyspnea and tachycardia. Anemia and fever may be present and edema and heart murmurs are occasionally found. The few electrocardiograms done in those cases reported in the literature show shallow T-waves, low voltage in all leads, and a tendency to left ventricular preponderance. There is often prolongation of the PR interval. Terminally, liver enlargement and edema commonly occur.

According to Kugel [9] roentgenograms demonstrate marked cardiac enlargement in all diameters with either right or left preponderance. Many times it is impossible to eliminate the presence of congenital heart disease roentgenographically. Roentgen examination was possible in the 25 day-old baby (Case 1) and in the 3-year-old boy (Case 3). In the first case (figure 1) films show marked cardiac enlargement in all diameters apparently involving both right and left heart though the right seems to be predominant. The cardiac shadow is not sharply outlined and there is fine mottling and decreased aeration throughout both lung fields. The trachea is in normal position in both antero-posterior and lateral projections (figure 2). There is no roentgen-ray evidence of emphysema. Antero-posterior (figure 3) chest films of the 3-year-old boy show marked cardiac enlargement with slight displacement of the trachea to the right. Here, too, both the right and left heart are enlarged, though in this case the lung fields are hyperaerated. In one of the films made just prior to this there is spontaneous pneumothorax on the left. The costal spaces are widened and there is flaring of the anterior ribs. The heart fills most of the chest and the conus pulmonalis is prominent. The terminal appearance of pneumothorax was due to rupture of a pleural bleb which developed as a result of emphysema.

The autopsy findings in these three cases are so similar that they may well be described together. In each there was marked cardiac hypertrophy without congenital anomaly or valve defect. Though hypertrophy was present in both right and left heart it was most marked on the right in all three instances. Chronic passive congestion of the liver was also a constant finding and in the case of the 3-year-old boy (Case 3) there was ascites and pleural effusion. In the other two autopsies the lungs were heavy, crepitation was diminished or absent, the cut surface was liver-like in consistency, yellowish-gray and edematous. Small grayish areas could be made out beneath the pleural surface in these two cases. The boy who lived three months after onset (Case 3) presented lungs which were voluminous and emphysematous, but the cut surface was firm in consistency. Small pleural blebs were encountered on the left. The thymus was large though not unusually so in the 11-month-old infant (Case 2) who died suddenly. In the two older children the thymus was atrophic.

FIG. 8. High power view of alveolar septum showing marked proliferation of alveolar histocytes and collagen formation. No capillaries are visible.

Sections of myocardium in each instance show fragmentation and degeneration of muscle fibers with occasional small areas of lymphocytic infiltration. There is some loss of cross striations in selected areas. Indigocarmine stains were negative for glycogen in one instance. This technic was not possible in the other two due to formalin fixation of tissue. There

was some endocardial thickening in both right and left ventricles, most marked on the right. Moderate perivascular fibrosis of the terminal branches of the coronary arteries was evident. The terminal branches of the coronaries were not remarkable.

The histological changes noted in the myocardium in all three hearts are quite similar. Though these changes conform in every respect to those described in cases of congenital idiopathic cardiac hypertrophy, there is little reason to believe that they represent other causes. Mitotic figures were seen in two of the hearts, but it has been shown [8] that this finding is not uncommon in cardiac hypertrophy in infants up to 20 months of age regardless of the cause of the hypertrophy. No mitotic figures could be found in the myocardium of the 3-year-old child (Case 3). The perivascular increase in collagen and patches of lymphocytic infiltration as well as fragmentation are changes not uncommon in myocardial hypertrophy occurring in nephritis, congenital heart disease or other primary diseases remote from the heart.

Little attention has been given to the histologic changes in the lungs in cardiac hypertrophy occurring in infants. Some [7, 8] have mentioned atelectasis though little import has been attached to it. Most of the lung changes have been attributed to primary cardiac pathology. McCordock and Muckenfuss [14] have presented evidence that interstitial pneumonitis occurs in two forms depending upon the concentration of virus. These conclusions are based on experimental and clinical observation. If experimental animals are given concentrated doses of virus there is an explosive type of histologic reaction with fibrin deposits in the alveolar spaces and necrosis of the wall. If given in more dilute form the histologic response within the alveoli is proliferative. Here the septa become thickened by proliferating histocytes, there is thickening of the adventitia of the vessels and mononuclear cellular infiltration of the walls of the bronchioles and arteries. The lining cells of the alveoli also proliferate. In the first type of reaction death occurs early due to what is usually termed "hemorrhagic virus pneumonia." In the proliferative type the process may resolve after a period of several weeks or may go on to chronicity.

Sprunt, Martin and McDearman [15] described much the same type of histologic reaction when they injected Bordet-Gengou bacilli intratracheally in the monkey and rabbit. Sections of the lung made soon after the injection showed alveoli filled with hemosiderin containing macrophages, and sections made 14 days after inoculation showed beginning proliferation of interstitial tissue. They found that heat-killed cultures produced a material which, by acting as a foreign body, produced lesions in the lungs similar to that seen with the virus itself. They showed that the avirulent form could also cause interstitial pneumonitis.

Although there has been considerable clinical and experimental observation on the pulmonary histology of virus disease in its early and fatal stages, little attention has been directed toward the lungs in those cases which re-

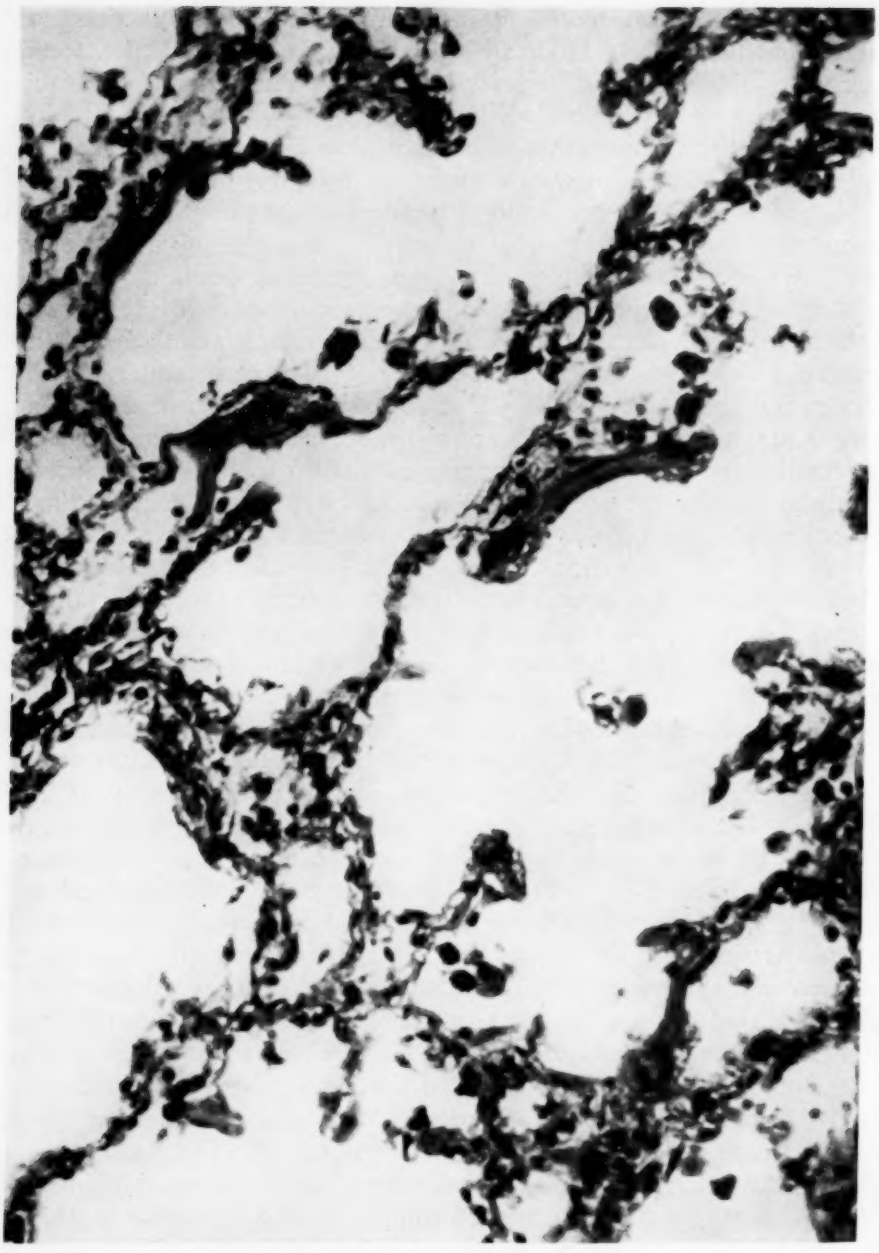

FIG. 9. Low power view of lung showing advanced emphysema with separation of the alveolar walls and thinning of the septae.

cover or become chronic. Kano-Ikeda [16] has described interstitial pneumonitis due to oil aspiration. The histology is very similar to that produced by filtrable virus.

Parker and Weiss [17] have described in detail the histologic changes taking place in pulmonary alveoli in far advanced mitral stenosis. Here, the first change is thickening of the capillary basement membrane which is later followed by edema, interstitial proliferation of cells and later in the most advanced stages by thickening of the alveolar basement membrane. They also describe thickening of the intima in branches of the pulmonary artery. In mitral stenosis there is marked increase in the number of alveolar capillaries which become coiled and dilated. They also point out that in cases of chronic pulmonary emphysema and repeated attacks of pneumonitis the same responsible factors are apt to coexist and hence pulmonary hypertension and arteriolar sclerosis are apt to occur. Snow and Cassasa [18] believe that emphysema commonly coexists with influenza and bronchopneumonia in infants. They state emphysema may be demonstrated in almost all infants with acute respiratory infection. They also think emphysema is obstructive and not compensatory. Shanks, Kerley and Twining [19] state that cardiac enlargement occurs in 40 per cent of cases of chronic emphysema with involvement of the right ventricle predominating, and that there is also enlargement of the conus pulmonalis in about half of these cases. The pulmonary changes in all of the three examples of cardiac enlargement forming the basis of this report are responsible for the cardiac hypertrophy and death. Many sections of these lungs were stained with hematoxylin and eosin, and Masson's trichrome stain. In the two cases with short clinical courses (Cases 11 and 12) the histologic changes are those of marked interstitial proliferation of alveolar phagocytes with thickening of alveolar walls. In most areas there is complete obliteration of alveolar spaces. In contrast to the picture described by Parker and Weiss [17] interalveolar capillaries are few in number and there is no evidence of thickening of the basement membrane. In the sections stained with Masson's trichrome methods there is definite evidence of laying down of collagen in the alveolar walls. Alveolar phagocytes are encountered in the few alveolar spaces which remain. Lymphocytic infiltration is seen throughout all of the thickened alveolar walls. Lymphocytic and monocytic infiltration is also found in the bronchial walls and in some areas there has been complete displacement of the alveolar walls by adult collagen. Most of the terminal arteries show thickening of adventitia and media. In an occasional small artery there is complete obliteration of the lumen by an old organized thrombus undergoing canalization. Sections made near the pleura show dilatation of vessels and diapedesis of red cells which must be interpreted as an attempt on the part of the bronchial circulation to compensate for the obstructive process taking place in the pulmonary circulation.

In the case of the 3-year-old boy (Case 3) whose clinical course was much more prolonged, the histologic picture is characteristic of chronic pulmonary emphysema. In many areas, however, there is evidence of preëxisting chronic interstitial pneumonitis. The relationship of interstitial pneumonitis

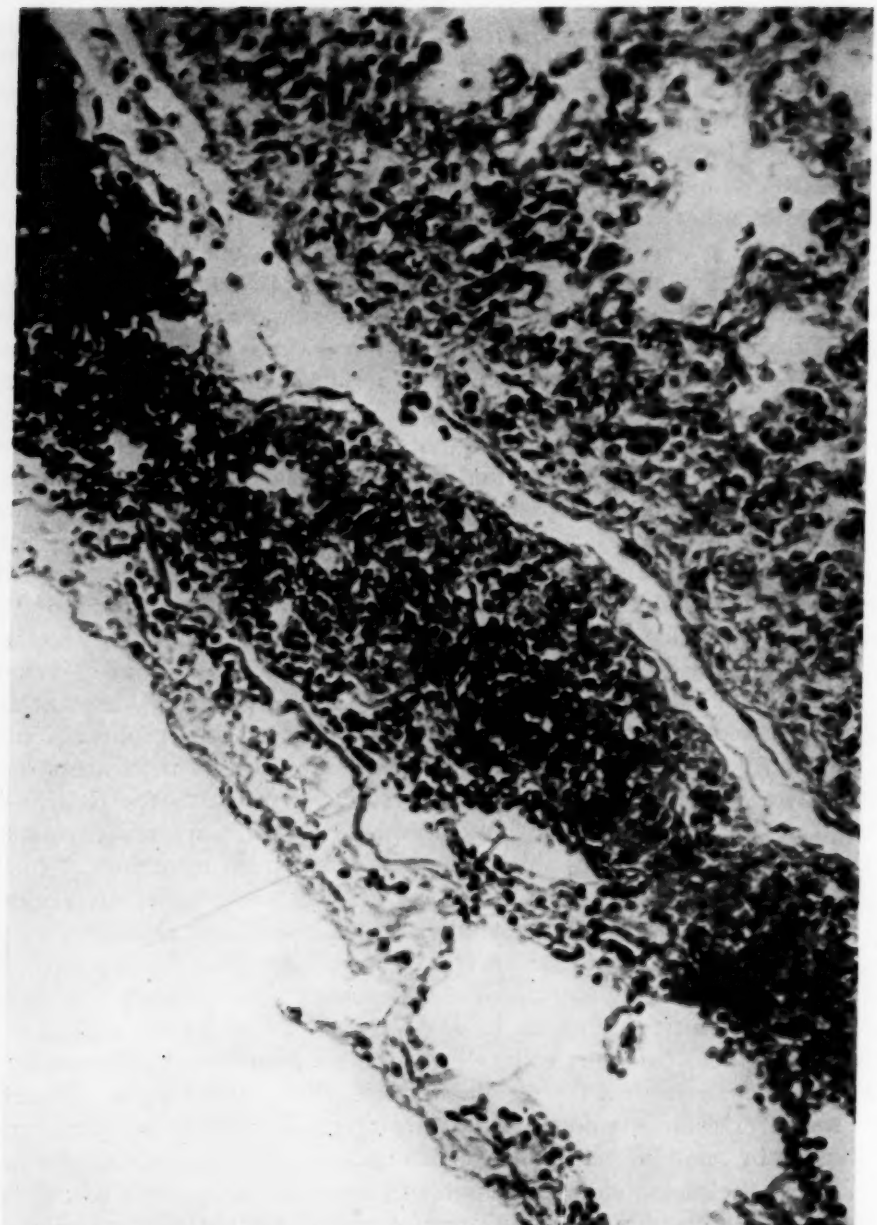

FIG. 10. Section including pleura showing marked dilatation and congestion of subpleural vascular supply indicating compensatory part taken by the bronchial circulation.

and pulmonary emphysema is clearly demonstrated. The general picture of the areas in these sections where interstitial pneumonitis persists is essentially the same as in the above described sections except that there is much more

collagen within the alveolar septa. In the emphysematous areas the capillaries are totally obliterated by collagen and remain as functionless as in the areas of cellular proliferation.

The effect of these changes on the right heart is essentially the same as those produced in advanced mitral stenosis in which there is elevation of pulmonary arterial pressure due to quite similar histologic changes in the alveolar walls and terminal pulmonary arteries. That these changes do not represent the result of long standing chronic passive congestion is evidenced by the presence of diffuse infiltration with lymphocytes and mononuclear cells and by the absence of proliferation and dilating alveolar capillaries. These capillaries in interstitial pneumonitis are closed or crowded out by the proliferating interstitial cells. That such alveolar changes produce increased pulmonary arterial pressure, however, is evidenced by the changes in the pulmonary arterioles, and the compensatory congestion and dilatation of the bronchial circulation beneath the pleura.

Attention has recently been directed toward the roentgen changes in acute and chronic interstitial pneumonitis. Reimann [21] recently described eight cases which he considered due to virus infection. Roentgenograms showed mottled increased density throughout both lung fields. Smiley and Showacre [20] described acute interstitial pneumonitis occurring in students at Cornell University. They pointed out that no roentgen-ray change is seen in the acute form until 48 to 72 hours have elapsed. They believe infection spreads from the hilum region outward. They also observed that the infection may clear up in from one to two weeks or may last up to three months. Snow and Cassasa [18] have emphasized the importance of emphysema, particularly where interstitial pneumonitis exists.

In those infants in whom cardiac enlargement exists it is important that careful attention be given the lung fields. If cardiac enlargement has occurred on the basis of interstitial pneumonitis it is likely that the pulmonary lesion has been present for some time. However, as pointed out by Parker and Weiss,[17] alveolar and arterial changes may take place in a relatively short period of time. Fine mottled increased density throughout both lung fields in films showing cardiac enlargement in infants will often be interpreted as chronic passive congestion, and unless observed over a considerable period of time with serial films, there is probably no definite method of making an accurate differential diagnosis between these two entities. Persistent fine mottling despite therapeutic measures for cardiac decompensation should direct one's attention to the possibility of chronic interstitial pneumonitis and in turn must be considered as a possible cause of cardiac hypertrophy.

Conclusion

Clinical and autopsy findings in three cases of cardiac enlargement in infants have been described. Evidence is presented to support the contention that, while the gross and microscopic changes in the heart are in each

instance consistent with the diagnosis of idiopathic cardiac hypertrophy, the primary cause of these changes is chronic interstitial pneumonitis with secondary cardiac hypertrophy. It is suggested that the rapidly dwindling group known as idiopathic cardiac hypertrophy will decrease still further if more attention is given the lungs clinically and at autopsy. Chronic pulmonary emphysema as the compensatory change in interstitial pneumonitis adds to the load placed on the right heart. Cardiac enlargement occurring in infants may be due to many and various causes. If such an entity as congenital idiopathic cardiac hypertrophy exists it must be so classified only after due consideration is given to all the possible causes.

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CASE REPORTS

COLD ALLERGY: REPORT OF AN UNUSUAL CASE*

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COLD allergy has been known since 1866, when Bourden [1] described urticaria and syncope due apparently to cold. However, in 1872 Blachez [2] gave the first classical description of urticaria from cold. Since then several other writers have reported cases of this form of allergy. Since 1924 Duke [3] has written voluminously on this subject, describing various forms of physical allergy, which he found to be not uncommon. He suggested the possibility that a histamine-like substance might be liberated locally and be responsible in some instances. Lewis [4] later showed the probable existence of such a substance. In 1929 Horton and Brown [5] reported a study of six cases of cold allergy in which attacks of syncope resulted from exposure of the skin to cold. They showed that if a tourniquet were applied to an extremity proximal to the chilled area the reaction would not occur. In 1936 Horton, Brown and Roth [6] published an outstanding contribution to this subject.

Duke's original method of testing for cold allergy consisted of either simply rubbing the skin with a block of ice or of alternating this with exposure to heat in order to produce a sudden change in temperature. He found that application of the opposite excitant quickly terminated the reaction (urticaria, asthma, sneezing, etc.). Horton, Brown and Roth placed the patient's hand and part of the forearm in water at about 9° C. (48° F.) for six minutes. A positive reaction consisted in the appearance three to six minutes later of local pallor which changed to redness, slight edema and an increase in local temperature. Sometimes a constitutional reaction followed with fall in blood pressure, rise in pulse rate, vertigo and even syncope. These manifestations were quickly counteracted by dipping the patient's hand in warm water or by applying a tourniquet above the elbow. Reënforcement of the reaction could be obtained by repeating the test while a tourniquet was applied to the arm above the elbow and then released. The subsequent reaction appeared sooner, was more severe and lasted as much as three times longer. The disappearance of the reaction occurred in six to eight minutes after its onset following the simple immersion of the hand and forearm in cold water.

The reactions to cold are thus seen to consist of contact reactions and reflex-like reactions (Duke). Syncopal reactions may be responsible for drowning (Horton, Brown and Roth). It has been suggested that chilblains may be due to cold allergy. Apparently, in rare instances, sensitization to cold may be passively transferred.

Treatment of uncomplicated cold allergy is often effective. For the attack the application of heat often dissipates the symptoms. Cure may be accom-

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plished in a few weeks by two methods. A hand is immersed in cold water for six minutes twice daily, the temperature of the water gradually being decreased from 65° F. to 45° F. as tolerance develops. The second method of treatment consists of injecting 0.1 mg. of histamine subcutaneously twice daily.

An excellent general summary of the subject of physical allergy is given by Vaughan.[7]

The following case is one of complicated cold allergy different from any thus far reported.

Case Report

Mr. G. W. C., a 53-year-old white married saleman, consulted one of us (E. W. N.) first in October 1935 complaining of "sciatic neuritis." He had had a similar attack in 1929 which lasted for three months in spite of the extraction of an abscessed tooth. Subsequently he had recurrent attacks which were not relieved by the extraction of other teeth. The worst attack occurred in 1932; this cleared up after a rectal abscess was discovered and incised. An orthopedist pronounced the "sciatic neuritis" sacroiliac strain. The attack in 1935 ceased after strapping of the pelvis with adhesive tape. Earlier illnesses were typhoid fever in 1892 and malaria in 1910 and 1920. Admission to the army had been refused in 1917 because of albuminuria, but life insurance had been granted in 1914 and was allowed again in 1934. For several years he had had intense bitemporal headaches not associated with nausea or vomiting.

In 1935 he stated that he had been troubled somewhat with hives which he had observed were worse when he ate something cold or exposed himself to cold atmospheres. In the summer of 1935 he had discovered that he could not go swimming without provoking an attack of hives.

In June 1936 his "sciatica" recurred more intensely and was accompanied by numbness and tingling of the right foot and dragging of this foot during walking. There was also numbness of the right hand and occasional difficulty in holding a pencil. This condition gradually subsided.

In September 1937 he complained of intense urticaria induced by cold and cold objects. For instance, sitting in an air-cooled theater first caused blueness of the left ear. Later, red blotches appeared on the feet and ankles, subsequently spreading to the thighs and waist. Still later the tongue, lips, nose and ears swelled up after eating ice cream or drinking cold water. From December 1937 on, the lesions on the ears and ankles appeared frequently with painful swelling and subcutaneous hemorrhages particularly into the helices of the ears during the acute phase. Blood cell counts were essentially normal. Between attacks purplish discoloration and pigmentation of the ankles was present.

In March 1938 he was examined at the Johns Hopkins Diagnostic Clinic. The following diagnoses were made: Chronic urticaria, purpura, hypersensitiveness to cold, low-back strain, benign prostatic hypertrophy, and external and internal hemorrhoids. It was noted that when a piece of ice was held next to the skin for 15 to 30 seconds a typical hive developed at the site of contact within 2 to 4 minutes. Attempts at passive transfer were negative. Dr. Leslie N. Gay suggested the use of histaminase or exposure of the hands to cold water. An interesting feature of these examinations was the urinalysis, which showed three plus albumin, numerous red blood cells and less numerous white blood cells. All other laboratory tests gave essentially normal results, including blood cell counts, platelet count, bleeding time and coagulation time.

Eight injections of histamine were given but were discontinued because of pronounced flushing of the skin and the formation of huge wheals at the sites of injection.

Purpuric spots similar to those on the ears began to appear more frequently on the ankles and remained for weeks as small, painful areas somewhat resembling areas of superficial gangrene. A purplish macular eruption extended from the ankles to the thighs and occasionally around the waist. Later it temporarily involved the hands, which on the slightest exposure to cold air became dusky and covered with painful hemorrhagic areas. In April 1938 the administration of histaminase was begun and continued for two months without improvement. Other forms of treatment employed later were subcutaneous injections of vitamin C, intravenous injections of typhoid vaccine and intravenous injections of 2 per cent salt solution, but the disease progressed and the legs became swollen and painful. In November 1939 the urine became scanty and smoky and was voided frequently and painfully. It contained four plus albumin and many red and white blood cells. Some specimens showed gross blood. This

FIG. 1. Purpuric lesions of the helix of the ear.

condition subsided in a month. A course of injections of snake venom was given with questionable improvement.

By March 1939 the disturbance had become so bad that even in warm weather the manifestations persisted, and the patient went about most of the time with ear muffs, gloves and woolen underwear and socks. Colder weather would cause an exacerbation, bringing on an "attack." The patient described this as follows: The ears would begin to itch and soon a throbbing pain would develop. Codeine might give some relief. The hands, feet and ankles quickly became swollen also, and the feet would feel numb. All affected parts would then quickly become bluish and later almost black. The swelling would subside in 12 to 18 hours, and scales would form on the helices of the ears in a few days (figure 1). Before the effects of one "attack" were over, another "attack" would occur. "Attacks" occurred about every 8 to 10 days. The urticaria had become much less prominent. The patient had lost about 13 pounds during the preceding years on account of the suffering. Sleep was restful but interrupted three or four times by urination because of the prostatic obstruction.

Examination at this time was not remarkable except for the appearance of the affected parts. The ears, fingers and feet were moderately swollen and there were discrete punctate hemorrhagic areas on the extremities, most numerous on the feet and ankles, but noticeable up to the thighs. The helices of the ears showed painful bluish-black hemorrhagic lesions and scales or crusts. Some of the lesions on the feet were superficially ulcerated. It was noticed that after the blood pressure reading had been made a wheal developed within 2 to 4 minutes at the site of pressure of the cool rim of the stethoscope. A small cube of ice was held against the skin of the chest and arms at various sites for from 10 to 20 seconds, and wheals developed at these sites in

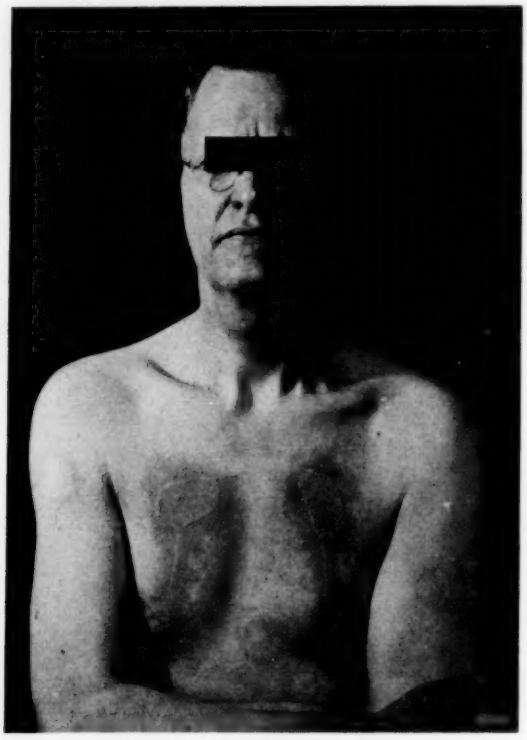

FIG. 2. Urticarial wheals on the trunk and arms produced by the application of cubes of ice. (Note the ear muffs almost constantly worn.)

from 2 to 4 minutes (figure 2). Where the water melted and ran down on the skin wheals also appeared. The cold-pressor test of Hines and Brown was performed. The basal blood pressure was 115 mm. Hg systolic and 70 mm. diastolic. The highest blood pressure reading was 145 mm. Hg systolic and 90 mm. diastolic, taken 1 minute after the immersion. There was no constitutional reaction, but the hand was reddened and slightly swollen. The patient said the hand throbbed.

A series of injections of testosterone propionate and later of estrogenic hormone were without apparent effect. A large amount of histaminase was again given without effect.

In October 1939 the patient was sent to the Mayo Clinic for investigation. The hand did not swell when immersed in cold water but the application of ice cubes to the skin still produced wheals. Regardless of "desensitization" with cold water over a

period of a month, the wheals could still be produced. There were no significant findings in the laboratory studies, which included blood cell counts, platelet and reticulocyte counts, blood smears, bleeding time, clot retraction time, vitamin C determination, and urine examination for lead and arsenic. The urinalysis was normal. A biopsy of the skin showed only the lesions of purpura.

The patient was urged to move to Arizona, which he did. Upon the advice of Dr. Bayard T. Horton of the Mayo Clinic he continued taking showers daily, beginning with warm water and allowing the water gradually to become cool. A report received on June 4, 1940, indicated that the patient was very much better. He was wearing short underwear for the first time in five years. The purpuric lesions of the ears had cleared up and he was using ear muffs only at night, the latter since it is quite cool at night in Phoenix. The ankles were still swollen, but the hemorrhagic areas on the ankles and feet had disappeared. The bluish discoloration which had extended up the legs and thighs was entirely gone. He had tested himself by applying a chilled bottle to the skin without a local reaction. He had not resumed working.

However, a report on September 16, 1941 was not so favorable. In a letter the patient stated as follows:

"I haven't made anything like the improvement I had hoped the summer heat out here would produce. However, the summer this year was not as hot as usual, so I am told. The highest official temperature this year has been 108 degrees, whereas the natives here tell me it usually goes to 118 and 120.

"I should have written to you long before this, but when one is sick everything is neglected. The swelling has left my feet and legs, but if I do much walking or sit still for any length of time my feet swell and cause me considerable pain. There is very little improvement in the color of my feet and legs, in fact I believe my right ankle is darker. It is almost black.

"I dread for the winter to come, as the least drop in temperature, or the least cool wind, causes my ears, feet and legs and sometimes my hands to hemorrhage. Was down town in one of the air-cooled stores today and my right ear began to tingle. When I got home I had a small new hemorrhage on it."

Comment

This is a case of cold allergy associated with purpura hemorrhagica of the affected, mainly acral, parts. The earlier urticarial reactions gradually subsided, leaving the purpuric manifestations of the ears, hands and feet as the outstanding feature of the case. There were no general or constitutional reactions on exposure to cold. At least two episodes are recorded, however, of hemorrhagic renal lesions which probably were purpuric in nature. No blood dyscrasia could be demonstrated. In spite of the definite cold allergy disclosed, there was no therapeutic response to the usual methods employed and found to be satisfactory in other cases of cold allergy. Apparently beginning as a simple cold allergy the condition finally became one of persistent purpura hemorrhagica of the acral parts with the evidence of cold allergy still persisting in the form of urticaria that could be induced locally by the application of cold objects to the skin. A similar case has not been previously reported.

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SYPHILITIC PAN-MENINGITIS (SO-CALLED CHRONIC HYPERTROPHIC SPINAL PACHYMENINGITIS) *

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THE case about to be reported belongs to the group of disorders erroneously referred to as " chronic hypertrophic spinal pachymeningitis." We say " erroneously referred to " because in most cases reported, the leptomeninges as well as the dura were adherent and involved in the pathological process. Since the detailed histological studies in our case provide additional evidence that the pathological process is something more than a hypertrophic " pachymeningitis " and since such cases are comparatively rare, a report of the present case seems justified.

Syphilis and tuberculosis have been considered the chief etiological agents in this disease, the former being by far the more common. Occasionally one encounters cases ascribed to trauma or to pyogenic infections. Invasion by pyogenic organisms is more prone to result in a *peripachymeningitis.* Peripachymeningitis was first described by Traube in 1871. In this condition there is combined inflammation of the spinal meninges (dura and arachnoid) and the epidural connective tissue situated between the dura and the periosteum of the vertebrae.[1] The main pathologic changes occur in the *perimeningeal* tissues which become infiltrated with pus or transformed into " sclerotic tissue." In syphilitic " pachymeningitis ", however, the process is restricted to the dural and intradural regions, the extradural tissues escaping. Both conditions may produce degenerative changes in the white matter of the spinal cord which, in some instances, resemble tabes dorsalis.

" Chronic hypertrophic spinal pachymeningitis " is essentially a chronic inflammatory reaction consisting of a fibrous hyperplasia of the dura, with perivascular and interstitial infiltration of lymphocytes and plasma cells. This infiltration is most intense near the inner layers of the dura, and is frequently continuous with the pathological process involving the underlying leptomeninges and spinal cord. The cord itself shows varying degrees of myelomalacia with demyelinization of various fiber pathways and degeneration of the ganglion cells. The cord changes are thought to be due either to constriction of the blood vessels

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supplying the cord by the thickened meninges or to a compression of the spinal roots with obliteration of the perineural subarachnoid spaces.

The symptoms of "chronic hypertrophic spinal pachymeningitis" present no pathognomonic features. They may vary from day to day, and in some cases have been mistaken for symptoms of hysterical origin. The distribution of neurologic signs is determined by the portion of the spinal cord that is involved. Although the disease has a particular affinity for the lower cervical region, it may develop at any level of the spinal cord. In our case the changes were confined exclusively to the lower segments. The disease cannot be regarded as an exclusively localized process, for it is merely a regional manifestation of a more generalized meningovascular syphilis. In many cases the symptoms are similar to those of spinal cord tumor with root pains, muscle atrophy and areflexia at the level of the lesion, and pyramidal signs below. There usually is ataxia and, with lesions in the cervical cord, there may be sensory dissociation. In some cases the symptoms may render difficult the differential diagnosis from syringomyelia. In fact, for many years there existed a controversy as to whether the thickening of the membranes was secondary to a condition of syringomyelia. This controversy can now be considered as settled since it is generally agreed that constriction of the cord vessels by the thickened meninges can produce central cavitation which may extend for a considerable distance from the lesion.

In the diagnosis of hypertrophic meningitis, examination of the cerebrospinal fluid may prove helpful. In many cases the Queckenstedt test is positive. Further, if a radiopaque medium is introduced into the spinal subarachnoid space and studied roentgenographically, the upper margin of the shadow is usually streaked and broken. This picture is distinct from that produced by an intraspinal tumor. Examination of the cerebrospinal fluid reveals an increase in the total protein. The fluid may be xanthochromic, and, in cases due to syphilis, the serologic tests are usually positive. However, as in our case, the fluid may, at first, give negative complement fixation tests.

Case Report

B. L., a single man aged 54 years, entered the Ancker Hospital in Saint Paul on June 9, 1938 complaining of pain in the back, pains in both legs, numbness of the feet, gait difficulty, sleeplessness, difficulty in urination, and constipation. He stated that six weeks previously he had "caught cold" and following this had noticed a sharp continuous pain in the left knee. This pain radiated up and down the lateral side of the leg, and was aggravated during cold damp weather but not by motion. For 10 days there had been pain in the right leg similar to that in the left, and both feet had been numb. During the three or four days preceding hospitalization there had been some difficulty in walking, but the patient was unable to state the exact nature of this interference. Constipation had been severe—"there seemed to be an obstruction in the rectum." There also was difficulty in emptying the bladder, but no involuntary urination. The past history was not contributory except for the fact that the patient had had gonorrhea 30 years before, and about 12 years before admission had suffered a penetrating wound of the left eye resulting in almost complete loss of vision and in the gradual development of an external squint.

The neurological examination revealed an exotropia of 25 on the left with an old, dense, sickle-shaped corneal scar, opacity of the lens, and an irregular iris. The right eye showed a 25 exotropia with ptosis of the lid and a paradoxical pupil. The right knee jerk was normal, but the left knee jerk and both ankle jerks were absent. There

was bilateral ataxia in the knee-heel tests; deep pain and position sense were lost in both feet. Light touch and superficial pain sense were impaired from the eleventh dorsal dermatome downward.

The physical examination was essentially negative except for a moderate degree of peripheral arteriosclerosis and a grade 1 enlargement of the prostate. Blood pressure was 150 mm. of Hg systolic and 96 diastolic, and tests for renal function gave normal results.

The cerebrospinal fluid was yellow in color, under 16 mm. Hg pressure, and showed no rise upon jugular compression. Globulin was 3 plus; there were 30

FIG. 1. Roentgen-ray showing the complete block of the Lipiodol between the second and third lumbar vertebrae. The irregular conical shape is very suggestive of adhesions.

lymphocytes per cu. mm.; the Wassermann reaction was negative, and the colloidal gold curve read 0000145300.

After some rather desultory treatment under which the pain and the bladder function improved, the patient was discharged from the hospital on August 4, 1938. He reappeared on September 28, 1938, saying that the pains in his legs were worse and his urinary retention was again troubling him. The examination gave essentially the same findings as on the previous admission. The patient was treated symptomatically. On January 18, 1939 a spinal tap produced deeply yellow fluid, and there was no rise on jugular compression. The cerebrospinal fluid chlorides were 613 mg. per 100 c.c., the protein 268 mg. per 100 c.c., glucose 204 mg. per 100 c.c. Wassermann reaction

4 plus, and the colloidal gold curve 0255543210. Treatment was continued with neoarsphenamine and sodium iodide.

On March 5, 1939, examination by another member of the staff showed both pupils to be fixed to light and the right to be larger than the left. The right fundus was normal and the left was not visualized because of the corneal scar. There was a left exophoria. The lower extremities showed pitting edema of both feet, with the right leg fixed in semiflexion, although the knee could be passively flexed to a slight degree. There was some movement of the left lower extremity at the hip, but the flexors and the extensors of the left leg were paralyzed. There was atrophy of both hamstring groups. Touch and pain sensation were impaired on the left side from the inguinal region downward, and on the right side from the knee down. There was impaired touch and pain sense over all of the sacral dermatomes bilaterally. A note was made to the effect that the eleventh dorsal spinous process seemed to be somewhat more prominent than the others. Spinal tap below the second lumbar spine gave

FIG. 2. Cross section through the region of the cauda equina. The entire spinal canal is filled by this chronic granulation. With careful study one can identify the thickened dura at the periphery.

clear, slightly yellow fluid under 110 mm. water pressure, rising to 180 mm. on jugular compression. Below the fourth lumbar vertebra the pressure readings were the same as below the second lumbar spine. The cerebrospinal fluid contained 182 mg. protein per 100 c.c., 162 mg. glucose per 100 c.c.; gave a positive Wassermann reaction, and a colloidal gold curve of 1554433100.

On March 10, 1939, after considerable discussion by various members of the staff, 5.0 c.c. of Lipiodol were injected into the lumbar subarachnoid space. Roentgenographic studies showed complete block in the ascent of the oil at the level of the inferior border of the disc between the second and third lumbar vertebrae. With the patient in the Trendelenburg position, the superior border of the oil was seen to be sharply irregular and conical, suggesting adhesions rather than protruding disc or tumor type of block (figure 1). The oil moved freely into the inferior sac with no appreciable disturbance in outline in the lumbosacral area. The spine showed a slight generalized hypertrophic arthritis, a marked accentuation of the lumbosacral angle, and a spondylolisthesis grade one. There was a spina bifida defect in the fifth lumbar and first sacral vertebrae.

On March 14, 1939, again after considerable discussion, an exploratory laminectomy was performed. The laminae of the second, third, and fourth lumbar vertebrae were removed, and an attempt was made to open the dura. The subarachnoid space was found to be completely obliterated except in the extreme upper and lower ends of the incision. The lipiodol was removed from the lower end of the incision. The dura was closed with interrupted silk sutures, and the muscles, fascia and skin were closed in layers. The patient rapidly failed and died six hours after the operation.

At *autopsy* the significant findings were confined to the nervous system. There were no evidences of visceral syphilis. The brain showed considerable accumulation

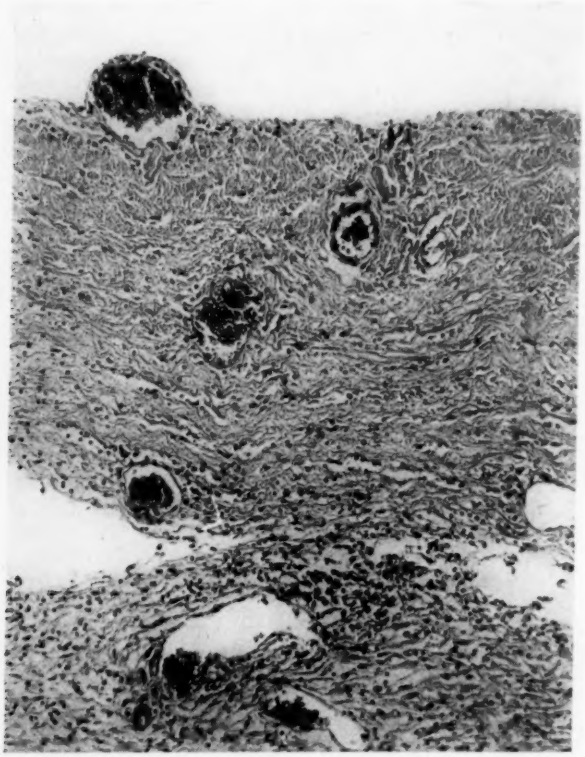

FIG. 3. Section through the thickened dura. The meningeal membrane is markedly thickened, fibrosed and partially hyalinized. Its inner surface is attached to the more cellular elements which fill the spinal canal.

of subarachnoid fluid. On cut section there was a small area of softening in the right basal ganglia. The brain was not studied microscopically. The external examination of the cord revealed a diffuse thickening of the pia-arachnoid, most marked in the lower levels. In the lumbar region the leptomeninges were firmly adherent to the dura, while in the region of the conus, these inner cord membranes had become completely obliterated by a firm rubbery mass which extended from the dura to the cord and was most extensive in the right lateral aspects of the cord. Here the spinal nerves were completely incorporated in the pathologic process. On the left lateral surface of the cord there was no such involvement, but the cord itself was moderately displaced and compressed to the left. Inferiorly in the region of the cauda equina this rubbery involvement increased in extent to include all structures in the spinal

canal so that the entire canal was filled by this rubbery substance which grossly had a lamellated appearance due to the presence of the numerous nerves whose outlines could hardly be made out. In this region the entire process was surrounded by a very greatly thickened dura which in some areas measured about 1 mm. in thickness and whose inner surface was firmly incorporated in the pathologic process (figure 2). The terminal 4 cm. of the cauda appeared free and uninvolved.

Microscopically, sections through the cauda equina in the regions of the most severe involvement revealed a thickened dura which could be clearly distinguished from the surrounding process. The dura had greatly thickened throughout its circum-

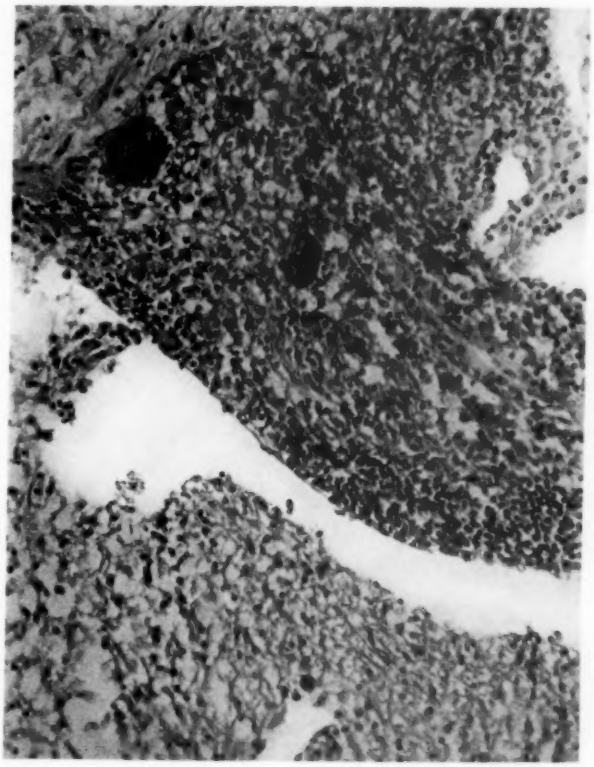

FIG. 4. Chronic granulation tissue. This tissue comprises the bulk of the inflammatory elements. Even with this moderate magnification one can identify lymphocytes, fibroblasts and giant cells.

ference and had undergone a dense fibrosis and in many areas a hyalinization (figure 3). Scattered throughout this altered dura were many scattered hemorrhages. The outer surface of the dura was invaded by numerous mononuclear cells, most of which remained localized to its superficial layers. The inner dural tissues presented a most extensive cellular alteration. This alteration was directly continuous with the extensive pathologic process which filled the spinal canal in this region (figure 4).

The entire area within the dura was replaced by a granulomatous process which had completely eradicated all structural architecture. It was impossible to identify the leptomeninges or the nerve roots (figure 2). Only in scattered areas could one observe with special stains an occasional naked axis cylinder or an axon surrounded by

the outline of a myelin sheath. The entire region was occupied by a chronic granulomatous process composed primarily of actively proliferating fibroblasts and strands and bundles of collagen. Intermixed with this connective tissue were numerous small lymphocytes, plasma cells, scavenger cells, and even an occasional leukocyte. This inflammatory process appeared to have extended outward from the inner layer of the dura with which it is intimately connected and to have penetrated the spinal canal, replacing the nervous structures (figures 2 and 3).

Necrosis was uncommon, and in the most severely involved regions only a single necrotic area was observed. This area was surrounded by a rim of small lymphocytes

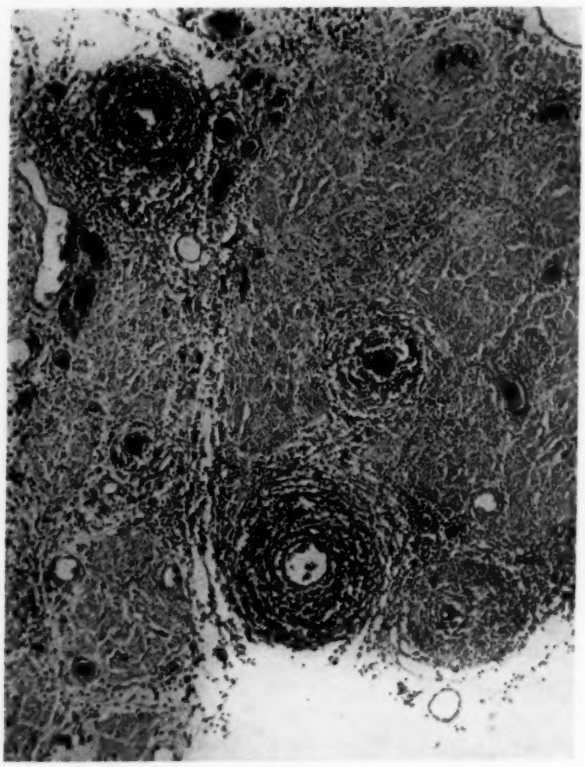

FIG. 5. Low magnification showing the extensive vascular involvement. These vessels present a typical Heubner's panarteritis. In one vessel the entire lumen has been occluded by an intimal proliferation.

and fibroblasts among which could be found an occasional giant cell. It had the appearance of a small gumma.

The blood vessels within this involved tissue presented very striking and characteristic findings. The larger vessels, especially those situated near the periphery and probably representing the meningeal vessels, showed mostly a fibrosis of the wall elements with a marked thickening of the vessel. The intima was proliferated and in many cases completely obliterated the vessel lumen. There was little or no cellular invasion into these vessels. The smaller vessels, especially those situated more centrally, presented the typical panarteritis described by Heubner (figure 5). All the wall elements were completely infiltrated by lymphocytes and plasma cells. In many

vessels the cellular reaction was so extensive that no vessel structure could be identified. Some of the vessels were occluded by endothelial proliferation (figures 5 and 6).

In the adjacent regions of the spinal cord the structural changes were very similar but less extensive. In spite of an almost complete demyelinization and a partial fragmentation of the axons, both cord and rootlet tissue could be identified in the region of the conus. In some isolated areas definite axons surrounded by moderately intact myelin were observed. However, throughout this region the granulomatous process infiltrated everywhere. In the lumbar cord the pathologic process was much less extensive. The cord architecture was intact; there was an extensive perivascular and

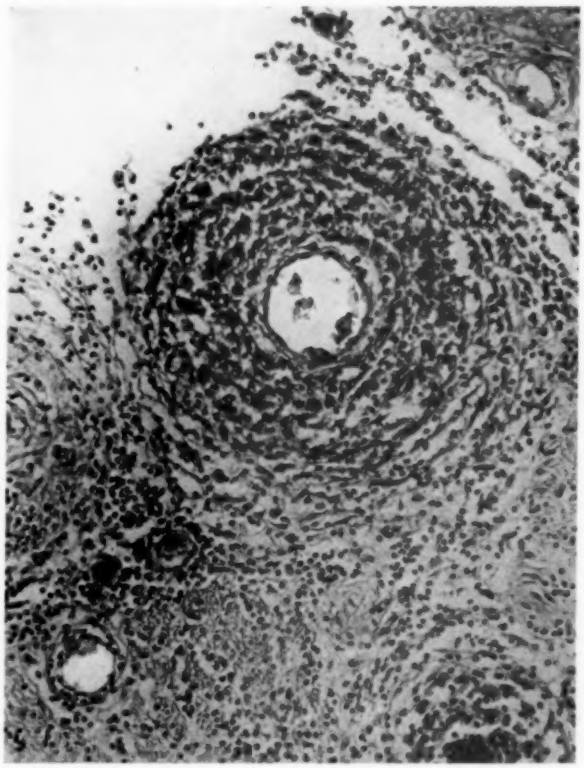

FIG. 6. Heubner's panarteritis, high magnification. Note the round cell invasion of all layers of the vessel wall. A beginning secondary fibrosis is becoming apparent. The vessel lumen is still patent.

diffuse lymphocytic infiltration involving both the gray and the white substance especially in the dorsal half of the cord. The meninges and the spaces along the dorsal aspect of the right side of the lumbar cord were obscured by the granulomatous process which in certain localized areas had penetrated through the pia into the posterior columns. Inflammatory tissue here resembled that already described in the region of the filum. The right posterior rootlets were enmeshed within the granulomatous tissue and showed extensive alterations. The rest of the rootlets in this region were intact. The leptomeninges were moderately fibrotic but otherwise normal.

All levels of the cord above the midlumbar region appeared to be intact histologically, except for a very mild thickening of the leptomeninges and a secondary involvement of the long sensory tract.

SUMMARY AND CONCLUSIONS

1. So-called *"chronic hypertrophic spinal pachymeningitis"* is in reality a pan-meningitis.

2. Syphilis and tuberculosis have been considered the chief etiological agents, the former being by far the more common.

3. The perimeningeal tissues are not involved.

4. In syphilitic pan-meningitis there is fibrous hyperplasia of the dura which is continuous with the pathological process involving the underlying leptomeninges and spinal cord. The cord shows varying degrees of myelomalacia with demyelinization of various fiber pathways and degeneration of ganglion cells.

5. While this disease has a particular affinity for the cervical region, it may develop at any level of the spinal cord.

6. A case of syphilitic pan-meningitis involving the lower portion of the spinal cord is reported with autopsy findings.

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SUBACUTE BACTERIAL ENDOCARDITIS CAUSED BY A HITHERTO UNDESCRIBED GRAM NEGATIVE COCCUS*

By GUSTAVE J. DAMMIN, M.D., *San Juan, Puerto Rico*

INTRODUCTION

THE following report concerns a case of calcific aortic stenosis with superimposed subacute bacterial endocarditis caused by a hitherto undescribed gram negative coccus. The literature on the occurrence and specific features of subacute bacterial endocarditis in the older age groups has recently been reviewed by Bayles and Lewis.[1] From a study of 28 patients over 40 years of age, they concluded that subacute bacterial endocarditis in this age group was (1) less frequently correctly diagnosed, that (2) heart failure and azotemia occurred more frequently, and that (3) bacteremia was more difficult to demonstrate.

The bacteriology of endocarditis was the subject of a recent study by Shiling.[2] Among the organisms cited as causative agents, there was one designated as a gram negative micrococcus, which was isolated from a case described by Coulter.[3] Shiling isolated from one of his cases of subacute bacterial endocarditis a gram negative coccus which could not be classified. The organism recovered from the case to be presented did not resemble the gram negative cocci isolated from previously reported cases. Since the organism had not been described previously, it was considered worthy of study.

* Received for publication August 20, 1940.

From the Medical Clinic and Pathological Department of the Peter Bent Brigham Hospital, Boston.

Case Report

The patient, P. F., was a 66-year-old white male who entered the Peter Bent Brigham Hospital on October 30, 1939, because of weakness and insomnia of one month's duration. There was no family history of rheumatic fever, scarlet fever or heart disease. The patient had always used tobacco, but never alcohol, to excess. As a child he had had scarlet fever and pertussis, and had been subject to frequent epistaxes. There was no past history of tonsillitis, chorea or upper respiratory infections. In 1896, at the age of 24, the patient had fever and migratory joint pains for which he was confined to bed for six months. He was told that he had rheumatic fever but that his heart was not affected. He had never had hemoptyses, precordial pain or attacks of syncope. There was no evidence that the patient had ever had gonorrhea or syphilis.

The present illness began about one month before admission when the patient contracted a cold which was accompanied by cough, sputum and nasal discharge. He complained of anorexia, insomnia, malaise and pains in the legs. During the week preceding admission, ankle edema and dyspnea on exertion appeared. There had been no recent noticeable weight loss.

Physical examination revealed a well developed, elderly, moderately dyspneic, undernourished man with normal temperature and pulse rate. Over the chest and extremities there were scattered telangiectases. There were no petechiae in the skin or mucous membranes. There were bilateral lenticular opacities which interfered with light perception and examination of the fundi. The throat was injected and the few remaining teeth showed extensive caries with associated pyorrhea alveolaris. The heart percussion outline showed enlargement to the left and downward. The rhythm was regular. There were no thrills. A high pitched early diastolic murmur was audible from the aortic area to the third left interspace. In the aortic area there was a rough systolic murmur of moderate intensity which was transmitted to the carotids. At the apex there was a long, loud systolic murmur. The pulmonic second sound was accentuated. The pulses were collapsing in type, but no capillary pulse was demonstrable. The blood pressure was 110 mm. of Hg systolic and 44 diastolic. Râles and dullness were present at both bases. Neither the liver nor the spleen was palpable. Crepitation was demonstrable in both knees. The finger tips were not tender nor was there clubbing of the fingers or toes. There was slight pitting over the tibiae.

The erythrocyte count was 2.73 million and the leukocyte count was 26,000 per cubic millimeter. The hemoglobin content was 60 per cent (Sahli). The differential leukocyte count showed 91 per cent neutrophiles, 5 per cent lymphocytes and 4 per cent monocytes. The mean corpuscular volume was 114 cubic microns, the mean corpuscular hemoglobin, 30 micromicrograms, the mean corpuscular hemoglobin concentration was 26 per cent, and the volume of packed erythrocytes, 31 per cent. The icterus index was 15. Blood Wassermann, Hinton and gonococcus complement fixation tests were negative. The urine was normal.

Admission diagnosis was rheumatic heart disease with aortic stenosis and insufficiency and subacute bacterial endocarditis.

The course was one of gradual downward progression. The fever initially was of a high grade remittent type which after five days became intermittent (see chart). The patient was coöperative on admission but soon became irrational and restless. Shaking chills accompanied the rises in temperature. A chest film showed the transverse cardiac dimension to comprise 65 per cent of the internal transverse diameter of the thorax, indicating cardiac enlargement. Fluoroscopy revealed an irregular mass of calcification in the region of the aortic valve. The electrocardiogram demonstrated left axis deviation. Albuminuria and microscopic hematuria were

present on several occasions. The plasma non-protein nitrogen rose from 19 to 41 milligrams per cent. The leukocytosis remained throughout the course (see chart). The capillary fragility as tested with the sphygmomanometer was normal. Sputum culture showed *B. proteus* and non-hemolytic *Staphylococcus aureus*. Two of the three blood cultures were positive. Digitalis, instituted on November 2, did not alter the downward trend of the patient's course. Because of rigidity of the neck which appeared on November 8, lumbar puncture was performed with, however, normal findings. Sulfanilamide was begun late in the course and did not influence the progressive decline. The spleen did not become palpable but petechiae appeared in the palpebral conjunctivae. On November 9, after sudden onset of respiratory difficulty, the patient died.

Autopsy was performed two hours post mortem. The skin and mucous membranes were pale and petechiae were noted in the conjunctivae and over the buttocks. There was moderate pitting edema over the sacrum.

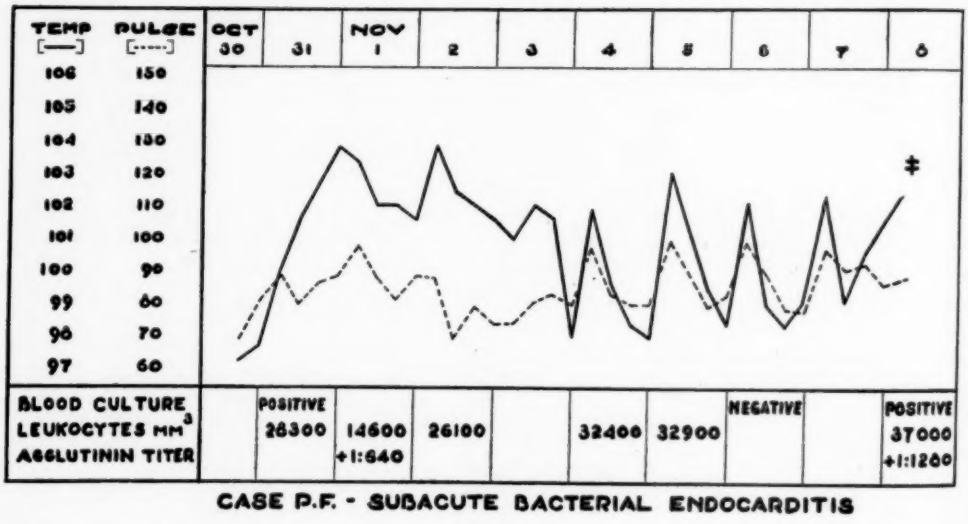

FIG. 1. Subacute bacterial endocarditis caused by a hitherto undescribed gram negative coccus.

The heart weighed 440 grams. There was left ventricular hypertrophy and the auricles were dilated. The tricuspid and pulmonic valves were normal. The mitral valve was thickened and opaque. The free edges were nodular but there was no calcification. The mitral orifice was not stenosed. The chordae tendineae and papillary muscles were normal.

The aortic valve presented on its left anterior cusp, a large, red, warty and friable vegetation measuring 3.0 by 1.5 centimeters. A smear of the cut surface showed numerous small gram negative cocci. On the right anterior cusp there was another warty friable vegetation measuring 1 cm. in diameter. Just proximal to this vegetation there was a small calcified plaque. There was a large calcified plaque in the aortic ring above the posterior cusp and another calcified area in the margin of the posterior cusp. The commissures between the aortic cusps were obliterated and the free margins were adherent 0.5 to 1.0 cm. radially from the aortic ring. The body of the aortic vegetation consisted of hyaline staining material with several dark staining areas (calcium) proximally and large lighter staining areas, consisting of masses of

bacteria, distally. The surface of the vegetation was covered by a layer of fibrin in which many erythrocytes and polymorphonuclear leukocytes were enmeshed (see photomicrograph).

Grossly, the myocardium showed no fibrosis or softening. Microscopically, there were many scattered clusters of polymorphonuclear leukocytes. There were also small areas of fibrosis showing infiltration with polymorphonuclear leukocytes.

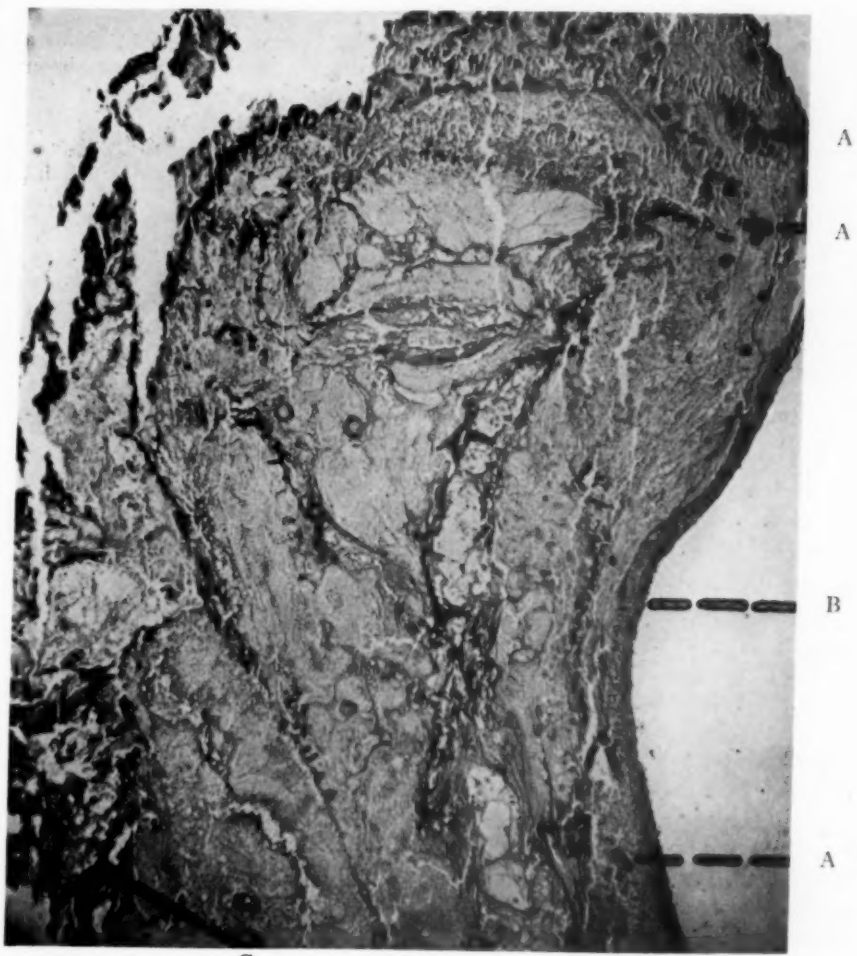

FIG. 2. (*A*) Masses of gram negative cocci. (*B*) Fibrin layer with enmeshed leukocytes and erythrocytes covering vegetation. (*C*) Calcific deposit in aortic valve.

The orifices and lumina of the coronary arteries were of normal patency throughout. In the aortic arch, 3 cm. above the aortic ring, there was an ulcerated calcified atheromatous plaque measuring 1 cm. in diameter.

The pericardial cavity contained 50 c.c. of cloudy yellow fluid which on smear showed many polymorphonuclear cells and minute gram negative cocci. The pericardial surfaces were injected. Microscopic section of the pericardium showed nu-

merous collections of polymorphonuclear cells and scattered hemorrhages. The epicardium also showed infiltration with polymorphonuclear leukocytes.

The right pleural cavity contained 250 c.c. and the left, 500 c.c. of yellowish, slightly turbid fluid. The right lung weighed 625, and the left, 540 grams. Extensive emphysema was present. The cut surfaces of the lungs were moist and congested, and showed scattered dark red mottled areas. Microscopically, the alveoli adjacent to the bronchioles were seen to be distended with polymorphonuclear and mononuclear leukocytes.

The spleen was firm and weighed 290 grams. There were no adhesions and the pulp was not soft. The liver weighed 1590 grams, was of normal consistency and showed no adhesions. The cut surface presented a nutmeg appearance. Microscopic sections showed the tributaries to the central veins distended with erythrocytes and the liver cells adjacent to the center of the lobule to be vacuolated and poorly staining.

The right kidney weighed 180, and the left, 200 grams. In the left kidney there was a yellow wedge-shaped infarct measuring 1 cm. in diameter. Subcapsular petechiae were present in both kidneys. Microscopically, the glomerular tufts were congested and the tubules distended with amorphous debris and erythrocytes.

The brain weighed 1200 grams. The vessels were normal but for a single atheromatous plaque measuring 1.5 mm. in diameter situated in the right anterior cerebral artery. There were no hemorrhages or aneurysms.

Anatomic diagnosis: Subacute bacterial endocarditis; rheumatic heart disease, inactive, with aortic stenosis and incompetency; calcification of the aortic valve; arteriosclerosis of the aorta; hydrothorax, bilateral, due to passive congestion; infarction of kidney, left, healed, due to embolism.

Bacteriology and Immunology

From the blood cultures taken on October 31 and November 8, the gram negative coccus to be described was isolated. The blood culture of November 6 was negative. The gram negative coccus was not recovered from the postmortem blood culture. One of the aortic vegetations was immersed in phenol, sectioned with sterile precautions, and the cut surfaces streaked on blood agar plates. In these cultures, the gram negative coccus was present but in a rougher phase than that recovered from the antemortem blood cultures. *B. proteus* was recovered from the sputum, stool and postmortem blood culture. Studies on the gram negative coccus and the *B. proteus* will be discussed separately.

Gram Negative Coccus: When this organism was isolated from the antemortem blood cultures (to be designated "AM"), it had the characteristics of an R (rough) phase organism. The growth on a blood agar plate after 48 hours' incubation at 37° C. in a moisture jar, consisted of minute, dark gray, dry, granular colonies measuring less than 1 mm. in diameter. Under the microscope the surface of the colony appeared dull and the edge was irregular. The colonies were firm in consistency and were removed from the medium with difficulty. The colonies produced neither green pigment nor hemolysis on blood agar. The organisms from these colonies did not enter into suspension in saline but precipitated spontaneously. Growth in dextrose serum broth was granular and produced minimal diffuse clouding. The organism cultured from the vegetation (to be designated "V") appeared to be in a still rougher phase and produced no clouding in dextrose serum broth.

For several months subsequent to initial isolation, these organisms were fastidious in their growth requirements. Serum or blood, as well as moisture, was

required. For the six months' period of observation, cultures of the "AM" and "V" organisms were transferred to freshly prepared blood agar plates or slants every 72 to 96 hours.

After three weeks of continued subculturing, the blood agar plate cultures of the "AM" organism showed occasional grayish white colonies which measured 1.5 to 2.0 mm. in diameter. Under the microscope the surface was even and the edge entire without projections. The colonies were moist in appearance and soft and butyraceous in consistency. In dextrose serum broth, these organisms produced a diffuse clouding and in saline remained in suspension. On blood agar, the colonies were surrounded by an area of greenish pigmentation, but no beta hemolysis. After three months, the blood plate cultures of the "V" organism showed colonies resembling the S (smooth) phase described for the "AM" organism above.

Morphology and Staining Characteristics: The "AM" and "V" organisms were morphologically identical. Throughout the six months' period of study, there was no change in the morphology of these organisms. Varying degrees of plemorphism were always present, however. The predominant form always was a gram negative coccus measuring 0.5 to 0.7 micron in diameter. There were occasional diplococcus and coccobacillary forms. The long axes of the paired cocci were not parallel, as with the meningococcus, but were in the same axis. These forms were more numerous when the organisms were cultured in liquid media. Old cultures showed swollen coccal forms measuring 1.0 to 2.0 microns in diameter. The organisms were constantly gram negative; at no time were gram positive forms present. They stained readily with methylene blue and showed no metachromatic staining. Using the Ziehl-Neelsen technic, they were not acid fast. The organisms were non-spore forming, non-motile and non-encapsulated.

Physical Growth Requirements: Optimum growth occurred at 37° C. in a moisture jar. Growth was equally good at 37° C. at 10 per cent carbon dioxide tension. Twenty-four hour dextrose broth cultures of the S phase of both the "AM" and "V" organisms did not withstand exposure to 56° C. for 15 minutes. There was no growth at 22° C. under either aerobic conditions or in a moisture jar. No growth occurred under strict anaerobic conditions, but there was moderate growth in a hydrogen-carbon dioxide-palladinized asbestos system.

Cultural Requirements and Reactions: As stated above, for several weeks to months after initial isolation, both organisms required either a serum or blood containing medium. Later, however, growth was accomplished in plain beef infusion broth and on plain agar, but growth was always scanty. Broth cultures invariably showed a tenacious pellicle adherent to the bottom of the tube. Good growth occurred in 0.15 per cent agar after 48 hours, but growth was slow on serum glucose agar and egg slants.* Very scant growth occurred on desoxycholate agar (Leifson). There was no growth on Simmons citrate agar, indicating an inability to utilize citrate. Moderate growth appeared on chocolate agar. The growth on Kligler's iron agar (Difco) indicated a production of acid but not hydrogen sulphide.

Twelve hour cultures of the "AM" and "V" organisms produced moder-

* These studies were performed at the National Institute of Health through the courtesy of Dr. Sara E. Branham.

ately active reduction of methylene blue. Catalase was demonstrable in all cultures from the time of initial isolation to the end of the period of study. Oxidase was tested for at monthly intervals with a 1 per cent solution of dimethyl-para-phenylene-diamine hydrochloride,[4] but was never demonstrable. Indol was not produced by either organism when tested for on five day peptone water cultures. Five-day 0.1 per cent potassium nitrate broth cultures of both organisms showed the presence of nitrite (Gries-Ilosva method).

Fermentation Reactions: Acid was produced on dextrose, levulose, maltose and mannose peptone water media. No gas was produced. Lactose, mannite, xylose and sucrose were not fermented. All fermentation reactions were observed over a period of 14 days.

Immunologic Studies: Both organisms were agglutinated in the same dilution by the patient's serum. The serum of November 1 was positive in a dilution of 1:640, that of November 8, in a dilution of 1:1280. Both 24 live broth cultures and saline suspensions of the "AM" and "V" organisms in their S phase were used in these agglutination studies. Incubation for 3 hours in a 37° C. water bath and overnight refrigeration were used. The same antigens were not agglutinated by normal control sera.

The patient's sera did not agglutinate *B. tularense* or *Brucella melitensis* in any dilution. The antigens of the "AM" and "V" organisms, used as described above, were not agglutinated by antisera for *B. tularense, Brucella abortus, E. typhosa,* Paratyphoid "A" and "B" and Proteus OX19.*

An antiserum was produced in a rabbit using the S phase of the "AM" organism. Live culture was administered intravenously on five occasions over a period of 10 days. At the end of this time the rabbit serum agglutinated both the "AM" and "V" organisms in a serum dilution of 1:2560.

The rabbit antiserum was used in an attempt to revert the S phase of the "V" organism to the R phase with the features it presented when first recovered from the aortic valve vegetation. Twelve hour broth cultures were transferred to whole rabbit antiserum and the rabbit antiserum diluted 1:1 with plain broth. Whole control rabbit serum, diluted control rabbit serum and plain broth tubes were also inoculated. These cultures were subcultured on blood agar plates each day for five days. However, growth on many of the subcultures was poor, and where growth was good, there was no evidence of reversion to the R phase. Saline suspensions of the "AM" organism, as well as live broth cultures were set up with therapeutic antimeningococcus serum.** This serum agglutinated both antigens in dilutions up to 1:128.

An antiserum was available, which had been prepared against a gram negative organism which had proved pathogenic for rabbits and which had been designated *Hemophilus cuniculi.* Neither the "AM" nor "V" organisms were agglutinated by this antiserum.

Animal Pathogenicity: A study of animal pathogenicity was made with both the "AM" and the "V" organisms in the R phase and were repeated when the S phase appeared. Large amounts of viable culture in both phases proved to be innocuous for white mice, guinea pigs and rabbits. Mice were inoculated intraperitoneally with 0.3 c.c. of a heavy broth suspension of 24-hour blood agar

** Supplied by the Antitoxin and Vaccine Laboratory of the Commonwealth of Massachusetts.

slant cultures. Guinea pigs received 0.6 c.c. of a similar antigen intraperitoneally and subcutaneously. Rabbits were inoculated intravenously with 2.0 c.c. of a similar broth suspension. The rabbits and guinea pigs had temperature elevations the day following inoculation, but survived for four weeks. After this period, they were autopsied. No lesions, including valvular lesions, were demonstrable. The mice also survived for four weeks and at autopsy presented nothing relevant. Neither the R nor the S phase proved to be pathogenic for the animals tested. In an effort to induce pathogenicity, mice were given large amounts of mucin-culture preparations, using both the "AM" and "V" organisms. Equal parts of 3 per cent mucin and a heavy broth suspension of 24-hour blood agar slant cultures were used. All the mice survived (two groups of four mice each) and after three weeks one mouse of each group was autopsied, again, however, with no lesions demonstrable.

B. proteus: By cultural and serological reactions, it was found that the same *B. proteus* had been recovered from the sputum, stool and postmortem blood culture. Saline suspensions of 24-hour plain agar slant cultures were used for agglutination studies. The patient's serum did not agglutinate the *B. proteus* obtained from any of the three sources. These antigens were not agglutinated by a high titer antiserum prepared against Proteus OX19. The patient's serum of November 1 and 8 showed a positive Weil-Felix reaction in a dilution of 1:80, using Proteus OX19. All agglutinations were incubated for three hours in a 37° C. water bath and read after overnight refrigeration.

The organisms from the three sources showed marked motility in 6-hour plain broth cultures, produced rapid stratiform liquefaction of gelatin and spread rapidly on plain and blood agar. Dextrose and xylose were fermented with formation of acid and gas. Acid was produced in sucrose after nine days. There was no action on lactose, maltose, mannite or salicin. Peptone water medium was used with incubation at 37° C. and observation for 14 days. Five-day peptone water cultures showed no production of indole. These reactions satisfy the criteria, as stated by Bergey,[5] for *Proteus mirabilis.*

Discussion

The main points of interest in this study were (1) the causative organism, (2) its transformation from an R to an S phase, and (3) the presence of a positive Weil-Felix reaction.

Since the positive Weil-Felix reaction is of but passing interest in this case, it will be discussed briefly. Only 2.8 per cent of routine sera will agglutinate Proteus OX19 in a dilution of 1:80.[6] We[7] observed that 40 per cent of patients with Proteus urinary tract infections showed positive Weil-Felix reactions and agglutinated their own *B. proteus.* In more than half of these instances, the Weil-Felix agglutinins could be absorbed out with the patient's own *B. proteus.* In this case, however, a positive Weil-Felix was present, but the patient did not agglutinate his own *B. proteus,* nor was it agglutinated by a high titer Proteus OX19 antiserum.

Of special interest in this case is the causative organism, an unclassified gram negative coccus, which was recovered from antemortem blood cultures and from the aortic valve vegetation in an R phase and which on continued cultivation

acquired the features of an S phase organism. Such transformation on continued cultivation was noted by Wilson [8] to occur among members of the genus Neisseria. The gram negative coccus described above possesses many of the features ascribed to the genus Neisseria and particularly to the *Neisseria meningitidis* or meningococcus. This is suggested by many of its growth characteristics and its agglutination by antimeningococcus serum. The genus Neisseria is not composed, however, of serologically distinct groups and cross reactions among the numerous species occur. The lack of pathogenicity for white mice, especially with the use of mucin-culture preparations, the negative oxidase reaction [4] and the morphology of the organism do not permit the identification of this gram negative coccus with the *Neisseria meningitidis*.

That the organisms recovered from cases of subacute bacterial endocarditis are often in the R phase was reported by Tunnicliff and Woolsey.[9] In a study of 26 cultures of *Streptococcus viridans* observed immediately after isolation from patients with subacute bacterial endocarditis, they found evidences of the R phase in 22 of the cultures. These observers suggested that the R element might be an essential factor in the production of endocarditis. As evidence for this, the studies of Rosenow [10] on the production of endocarditis in rabbits using streptococci possessing features of the R phase, were cited.

Summary

A case is presented of subacute bacterial endocarditis superimposed on rheumatic heart disease with calcific aortic stenosis in an elderly male.

The causative organism, a gram negative coccus which we have been unable to classify, was recovered from antemortem blood cultures and was demonstrable in the aortic valve vegetations by smear, and by cultural and histological methods. The causative organism was agglutinated in high dilutions of the patient's serum.

The gram negative coccus, when first isolated, presented the features of an R phase organism, and during the course of continued cultivation, acquired those of an S phase organism.

The morphological, cultural and serological characteristics of this gram negative coccus suggest, but do not permit an unreserved identification with the genus Neisseria.

Note: The author is grateful to Dr. Charles A. Janeway for his kind assistance in the preparation of the material and the manuscript.

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EDITORIAL

THE ASSOCIATION OF ACUTE PANCREATITIS WITH DIABETES MELLITUS

THE association of the pancreas and, more specifically, of the islet tissue with the diabetic state was realized as the result of animal experiments carried out some 30 years before the discovery of insulin. The further interrelationships between the pancreas and the disease diabetes mellitus in man we are still in the process of uncovering. Among these are the various associations between acute pancreatitis and diabetes mellitus.

It has frequently been observed that during acute pancreatitis a temporary glycosuria may appear. Egdahl [1] reported an incidence of 5 per cent in 105 cases of acute pancreatitis. Guleke,[2] cited by Walzel, found glycosuria in about 10 per cent of his cases. Shumacker,[3] in a review of the literature, found 78 instances of glycosuria in 700 reported cases of acute pancreatitis, an incidence of 11 per cent. He also found that 28 of 55 cases had blood sugar levels above 200 mg. per cent.

It is commonly assumed that hyperglycemia and glycosuria during acute pancreatitis are due to destruction or dysfunction of islet tissue resulting from the diffuse necrosis, edema and hemorrhage in the pancreas. Gray and his coworkers,[4] however, have expressed the belief that the rise in blood sugar levels may result from hepatic dysfunction; and Brocq and Varangot [5] have advanced the theory that the large amounts of trypsin liberated in acute pancreatitis might have some inhibitory action on insulin.

As opposed to the relative frequency of these reports of disturbed carbohydrate metabolism during the acute stage of pancreatitis, there is a scarcity of published instances of permanent diabetes mellitus following upon recovery from acute pancreatitis. Bernhard,[6] however, in studying 50 cases of operative recovery from acute pancreatitis, found that diabetes mellitus had

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appeared in five instances. It is of interest that in a number of cases of this type an interval of months or years intervened between the attack of pancreatitis and the appearance of diabetes. This creates a natural doubt as to whether the pancreatic injury was the cause of the later diabetes. It seems probable, however, that in such instances the acute pancreatitis is followed by a progressive fibrosis and reduction of islet tissue.

Aside from the effect of acute pancreatitis in producing temporary or permanent derangements of carbohydrate metabolism, there is another association between diabetes and pancreatitis which has great interest. From available pathological studies it appears that the diabetic is more subject to attacks of acute pancreatitis than the non-diabetic patient. Warren,[7] in a study of the pancreas in 484 cases of diabetes mellitus, found acute pancreatitis in four cases, pancreatic apoplexy in two cases, and subacute pancreatitis in six cases. This high incidence (2.4 per cent) is approximately eight times the incidence of pancreatitis found by Hamperl [8] in a series of 20,000 autopsies. The explanation for the susceptibility of the diabetic to acute pancreatitis is not clear. Rich and Duff,[9] in this connection, referred to the statement of Babkin [10] that in rabbits hyperglycemia results in the production of an extremely ferment-rich pancreatic juice. Such a juice might, in the presence of minor pancreatic injury or duct obstruction, predispose to autolytic changes in the gland. The presence of ferment-rich pancreatic juice in human diabetics has not, however, been demonstrated.

The occurrence of acute pancreatitis in the diabetic has a very definite clinical importance, since the patient is precipitated into severe acidosis or coma. This combination of diabetic coma and acute pancreatitis is not rare. Root,[11] in autopsies on 26 patients dying in diabetic coma, found four instances of acute pancreatitis. Warren,[7] in 121 cases of coma death, found at autopsy 11 instances of acute or subacute pancreatitis. Bowers and Atkins,[12] in 17 autopsies on cases of diabetic coma, found three examples of acute interstitial pancreatitis. Joslin [13] states that acute pancreatitis should be considered in any case of diabetic acidosis that does not react favorably to intensive insulin therapy.

[7] Warren, Shields: The pathology of diabetes mellitus, 1938, Lea and Febiger, Philadelphia.

[8] Hamperl, H., quoted by Böse, H.: Die Pankreatitis. Übersichtsreferat, Zentralbl. f. Chir., 1936, lxiii, 261–263.

[9] Rich, A., and Duff, G.: Experimental and pathological studies on the pathogenesis of acute hemorrhagic pancreatitis, Bull. Johns Hopkins Hosp., 1936, lviii, 212.

[10] Babkin, B. P.: Blood sugar concentration and the external secretion of the pancreatic gland, Jr. Am. Med. Assoc., 1935, cv, 1659–1662.

[11] Root, H. F.: Diabetic coma and acute pancreatitis with fatty livers, Jr. Am. Med. Assoc., 1937, cviii, 777–780.

[12] Bowers, John Z., and Atkins, John L.: Acute pancreatitis with diabetic acidosis occurring in the course of diabetes mellitus. (Unpublished.)

[13] Joslin, E. P.: Treatment of diabetes mellitus, 1937, Lea and Febiger, Philadelphia, p. 559.

It is obvious that the diagnosis of pancreatitis in the presence of diabetic coma presents serious difficulties. The use of the amylase test in blood and urine may afford data which will usefully supplement the clinical symptoms and signs. In certain instances, however, the findings by the blood amylase test may be deceiving. Further clinical and pathological studies are needed in this field.

REVIEWS

The Pharmacological Basis of Therapeutics. By Louis Goodman, M.A., M.D., and Alfred Gilman, Ph.D. 1383 pages; 26 × 18.5 cm. The Macmillan Company, New York City. 1941. Price, $12.50.

In writing this comprehensive treatise on pharmacology the authors have had three objectives in mind: first, the correlation of pharmacology with the related medical sciences; second, the reinterpretation of the action and uses of drugs from the point of view of the important advances in medicine; and third, the placing of emphasis on the application of pharmacodynamics to therapeutics. The book has been divided into 16 sections, based largely upon the physiological systems of the body upon which drugs act. In addition there is an appendix in which the principles of prescription writing are discussed.

The authors, in preparing this subject matter for the various sections of this book, have made an exhaustive survey of the literature and have not only presented cogent data from various scientific journals but have critically evaluated the experimental work recorded. Historical sketches of the first use of various drugs are found throughout the book particularly in the field of anesthesia and in the development of autonomic drugs. In this the authors have shown a felicity of style uncommon to books of this character.

The physiological approach to many of the subjects is to be commended, particularly the authors' treatment of the pharmacology of the autonomic nervous system where the latest theories of the action of drugs on organs of autonomic innervation are discussed and elucidated from a pharmacologic standpoint.

The book is extraordinarily recent in its references which are given in great detail, and the latest subject matter in the field of pharmacology dealing with the adrenal-cortical hormone, sulfonamide derivatives and vitamins appears to be brought up to the very time of the publication of the book.

The reviewer highly commends this book to the practicing physician and to students in pharmacology or medicine as a standard reference and text for the application of the use of drugs in the treatment of disease.

J. C. K., Jr.

Bacillary and Rickettsial Infections. By William H. Holmes, M.D. 676 pages; 24 × 16 cm. The Macmillan Company, New York City. 1940. Price, $6.00.

This is a pleasant, well bound book inescapably reminiscent of Zinsser. Used as a textbook by the author, it combines points of view and is written in a style more literary than that of the usual textbook. The clinical implications are succinctly indicated, and logical therapies are mentioned briefly. Quotations of sources are used, and each seems chosen for its literary style, as well as for medical priority. The Bible and the ancient Greeks are heavily leaned upon, and historical background is journalistically stressed. Except for having specific and accurate data instead of generalities, it might well be a popular volume. Such gallant treatment builds two aspects of bacteriology into a full-sized book. With the world in camps again, however, and the danger of plague so near to us all, it is perhaps not out of proportion. This is a book that can be recommended to students with time to read it, and to lay persons interested in the background of epidemics and in a wellbred perspective on modern medicine.

C. A.

Cardiac Clinics. By FREDERICK A. WILLIUS, B.S., M.D., M.S. in Med. 276 pages; 24.5 × 17 cm. C. V. Mosby Co., St. Louis, Missouri. 1941. Price, $4.00.

This book is an accumulation of the "Cardiac Clinics" which have appeared previously in the Proceedings of the Staff Meetings of the Mayo Clinic.

All of the common and a few of the rare diseases of the heart are considered briefly. Each type of cardiac disease is illustrated with several cases from the files of the Mayo Clinic. A synopsis of the history, physical examination, and laboratory findings of each case is given. This is followed by a concise, formal discussion in which the pertinent diagnostic features are recapitulated and their practical significance stressed. Whenever possible the author has amplified the case studies by noting the important pathological findings. The case studies are usually supplemented with an informal set of questions and answers concerning the particular case or the general type of heart disease under discussion.

The author advises caution in making a diagnosis on the basis of a few isolated findings. He stresses the point that a case may be quite atypical, and that supposedly pathognomonic criteria may either be absent or refer to more than one entity. However, many practical and valuable diagnostic and prognostic maxims are mentioned.

There is a commendable effort made to explain briefly the mechanism by which the pathological physiology occurring in cardiac disease produces abnormal symptoms and physical signs. The chapters on "Functional States" and "Treatment and Management" are exceptionally good.

There are a few statements which justify mild adverse criticism. On page 37, in a discussion of a metastatic adenocarcinoma of the pericardium, the primary site is stated as being in a bronchial node. This is not in keeping with accepted pathological teachings. On page 77 the term *malignant endocarditis* is stated as being synonymous with *subacute bacterial endocarditis.* Although this is permissible, and although the ultimate malignancy of *subacute bacterial endocarditis* is unquestioned, yet the consensus of opinion associates *malignant endocarditis* with *acute bacterial endocarditis* rather than with *subacute bacterial endocarditis.* On page 109, in a discussion of gallop rhythm, the author states that the mesodiastolic type occurs "between the first and second heart tones." This obviously was meant to be "between the second and first heart tones." The author's effort to explain the preponderance of coronary thrombosis in males as compared with females seems a bit too theoretical. He believes that coronary sclerosis and thrombosis represent a metabolic disturbance in which the blood lipoids are increased. He argues further that the female is better able to cope with increased blood lipoids than the male, since she adequately stores and handles physiological increases in blood lipoids during pregnancy.

This book does not assume the exhaustive scope or character of a textbook, but could be used beneficially by the medical student and busy practitioner as a practical companion to a cardiology text. The style is concise and forceful. The lucid manner of presentation promotes easy reading.

E. T. L.

Infantile Paralysis—A Symposium Delivered at Vanderbilt University, April, 1941. 239 pages; 23.5 × 16 cm. National Foundation for Infantile Paralysis, Inc., New York City. 1941. Price, $1.25.

This book is composed of six lectures delivered at Vanderbilt University in April of 1941 on the history, etiology, immunology, pathology and pathogenesis, epidemiology, and treatment of poliomyelitis, by Drs. Paul F. Clark, Charles Armstrong, Thomas M. Rivers, Ernest W. Goodpasture, John R. Paul, and Frank R. Ober. The purpose of this symposium has been to compile and evaluate the important publications on poliomyelitis and to serve as a stimulus and guide for further investigation.

Experimental studies on poliomyelitis have been limited due to the expense involved when working with monkeys. All other laboratory animals proved unsatisfactory. A possible solution to this problem is offered by the successful transfer of a strain of poliomyelitis virus from the monkey to cotton rats and then to white mice without loss of virulence. This method offers an opportunity for extensive investigation with minimal expense. The interpretation of results is beset with difficulties due to the presence of different strains of poliomyelitis virus. There are also the hazards involved when trying to apply data derived from animals to the human disease.

There is a conflict of opinion concerning the protective antibodies present in the blood serum of many persons who give no history of having had poliomyelitis. Some feel that they are of a nonspecific character, whereas others contend that they result from subclinical infections. It is of interest to note that in some instances the neutralizing antibodies do not appear in the blood until long after recovery from the disease, and that the paralytic form of poliomyelitis may develop even though neutralizing antibodies are present in the blood serum.

There is a difference of opinion as to the mode of transmission of the disease. The concept of neuron transmission is based upon work done using the *Macaca rhesus*. The virus was found to pass from the nares along the olfactory nerves to the olfactory bulb and then along the olfactory tract to the brain. Recent work with the *Macaca cynomolgus* reveals that this species is susceptible to intestinal inoculation. The virus has been found in the stools of active cases, recovered cases, and contacts. The virus is present in city sewage and has been found in water. The spread of the disease along waterways has been observed.

The reader will find in this book a stimulating survey of the established facts and unsettled problems of this interesting and in many respects baffling disease.

E. F. C.

The Doctor and the Difficult Child. By WILLIAM MOODIE, M.D., F.R.C.P., D.P.M. 214 pages; 21 × 14 cm. Commonwealth Fund, New York City. 1941. Price, $1.50.

This book is written in a simple, elementary fashion for the purpose of instruction in child guidance. It is fairly evenly divided into two main sections. The first has to do with instruction in the recognition of the problem, history taking, examination, and treatment. The second part deals with more specific problems of behavior, i.e., stealing, lying, feeding difficulties, nervousness, sex difficulties, etc.

Because of the variety of symptoms in behavior problems, no satisfactory system of classification or diagnosis will ever be possible. This difficulty in organization is noticeable throughout the book. It must once more be emphasized that the book fulfills its object in being elementary.

W. M. S.

COLLEGE NEWS NOTES

Gifts to the College Library

We gratefully acknowledge receipt of the following gifts donated to the College Library of Publications by Members:

Books

Dr. Jacob Segal, F.A.C.P., New York, N. Y.—"Diseases of the Respiratory Tract"; Department of Experimental Medicine, George Washington University School of Medicine, Washington, D. C.—a bound volume of 32 reprints, many of which were written by members of the College.

Reprints

Dr. Frank N. Allan, F.A.C.P., Boston, Mass.—1 reprint;
Dr. Thomas W. Baker, F.A.C.P., Charlotte, N. C.—3 reprints;
Dr. Edward G. Billings, F.A.C.P., Denver, Colo.—1 reprint;
Dr. L. Minor Blackford, F.A.C.P., Atlanta, Ga.—2 reprints;
Dr. Edward N. Chapman, F.A.C.P., Colorado Springs, Colo.—1 reprint;
Dr. Hyman I. Goldstein (Associate), Camden, N. J.—2 reprints;
Dr. Charles E. Lyght, F.A.C.P., Northfield, Minn.—1 reprint;
Dr. Robert C. Page (Associate), Mount Vernon, N. Y.—2 reprints;
Dr. R. Henry Temple (Associate), Kinston, N. C.—1 reprint;
Dr. J. Lawn Thompson, Jr. (Associate), Washington, D. C.—1 reprint.

On September 10, 1941, Dr. George R. Herrmann, F.A.C.P., Galveston, Tex., addressed the Sociedad Mexicana de Cardiologia at Mexico City, D. F., on the subject of "The Blood and the Kidney in the Maintenance of Circulatory Equilibrium," reporting work done with Dr. George M. Decherd, Jr., F.A.C.P., Galveston, Tex., and D. B. Calvin, Ph.D.

Dr. Ignacio Chavez, F.A.C.P., Mexico City, D. F., presided. Dr. Francisco de P. Miranda, F.A.C.P., College Governor for Mexico, interpreted and discussed the paper.

Dr. Burton L. Zohman, F.A.C.P., has been promoted from Associate in Medicine to Assistant Clinical Professor of Medicine at the Long Island College of Medicine, Brooklyn, N. Y.

Captain Frederick L. McDaniel, F.A.C.P., (MC) U.S.N., has been appointed executive officer of the U. S. Naval Hospital at Great Lakes, Ill.

Captain McDaniel has been a member of the Medical Corps of the U. S. Navy since 1917. During the first World War he was on duty with U. S. destroyers operating in European waters, and, following the cessation of hostilities in 1918, saw service in the West Indies, Washington, D. C., and with the Pacific Fleet.

On September 4, 1941, Dr. Bernard I. Comroe, F.A.C.P., Philadelphia, Pa., addressed the American Congress of Physical Therapy in Washington, D. C., on "Physical Therapy in Arthritis."

The Association of Military Surgeons of the United States will hold its annual meeting in Louisville, Ky., October 29 to November 1, 1941. This meeting will be a most timely and interesting one. War medicine and surgery have changed considerably since the previous emergency. Mechanization of armies and air bombardments have created new and difficult problems.

All members of the medical profession are invited to attend as guests, for there will be something of special interest to everyone.

The following members of the College will present papers at this meeting: Rear Admiral Ross T. McIntire, F.A.C.P., Surgeon General, U. S. Navy; Major Frank B. Wakeman (Associate), (MC) U. S. A., representing Major General James C. Magee, F.A.C.P., Surgeon General, U. S. Army; Major General Charles R. Reynolds, F.A.C.P. (MC) U. S. A., Retired, Harrisburg, Pa.; and Colonel Leonard G. Rowntree, F.A.C.P., (MRC) U. S. A. General Reynolds is chairman of the program committee.

During June the Florida Medical Association and the Florida State Board of Health sponsored their 9th annual series of postgraduate courses for physicians, at Jacksonville, Fla. Among the members of the College who conducted these courses were:

Dr. Henry M. Thomas, Jr., F.A.C.P., Baltimore, Md.—Medicine;
Dr. Charles F. Mohr (Associate), Baltimore, Md.—Venereal Diseases;
Col. Luther R. Poust, F.A.C.P., (MC) U. S. A.—Military Medicine;
Comdr. Eben E. Smith, F.A.C.P., (MC) U. S. N.—Military Medicine.

Dr. Harry L. Alexander, F.A.C.P., has been promoted to Professor of Clinical Medicine at Washington University School of Medicine, St. Louis, Mo. He has also been appointed Acting Head of the Department of Internal Medicine at the University, succeeding Dr. David P. Barr, F.A.C.P., who resigned to accept an appointment as Professor of Medicine at Cornell University Medical College, New York, N. Y.

The Oregon State Medical Society held its 67th Annual Session and Post-graduate Assembly in Portland, September 3–6, 1941. Among the members of the College who spoke at this meeting were:

Dr. Milton B. Cohen, F.A.C.P., Cleveland, Ohio—"Nature of Allergy, Its Pathology and Mechanisms of Its Production," "Management of Patients with Asthma, Hay Fever and Other Allergic States," and "Growth Disturbances Produced by Allergy";

Dr. Henry J. Tumen (Associate), Philadelphia, Pa.—"Diagnosis and Treatment of Jaundice," "Management of Patient with Irritable Colon," and "Clinical and Gastroscopic Features of Chronic Gastritis."

Dr. M. Herbert Barker, F.A.C.P., Chicago, Ill., spoke on "Chemotherapy—Sulfonamide Group," and Dr. Harold Feil, F.A.C.P., Cleveland, Ohio, spoke on "Cardiovascular Disabilities of Railway Employees—Problems of the Consultant: A Review of Eight Years' Experience" at the 52nd Annual Meeting of the American Association of Railway Surgeons, held in Chicago, Ill., September 8–10, 1941.

The second triennial reunion for alumni of the University of Michigan Medical School and former staff members and house officers of the University Hospital was

held in Ann Arbor, Mich., October 2–4, 1941. Among the alumni speakers who are members of the College were:

Dr. Charles L. Brown, F.A.C.P., Philadelphia, Pa.—"Clinical Aspects of Osteoporosis";

Lt. Col. Joseph R. Darnall, F.A.C.P., (MC) U. S. A.—Concerning Army Medical Service";

Dr. Robert T. Monroe, F.A.C.P., Boston, Mass.—"Old Age";

Dr. Walter M. Simpson, F.A.C.P., Dayton, Ohio—"New Developments in the Diagnosis and Treatment of Brucellosis."

The 7th Annual Piedmont Post Graduate Clinical Assembly was held at the Anderson County Hospital, Anderson, S. C., September 9–11, 1941. Among the members of the College who spoke at this meeting were:

Dr. Franklin B. Peck (Associate), Indianapolis, Ind.—"Therapeutic Application of the Various Insulins";

Lieut. Col. Elias E. Cooley, F.A.C.P., (MC) U. S. A.—"Medico-military Problems of the Moment";

Dr. Kenneth M. Lynch, F.A.C.P., Charleston, S. C.—"Pathology of Uterine Carcinoma";

Dr. H. Sheridan Baketel, F.A.C.P., Jersey City, N. J.—"The Future Economic Status of the Physician";

Dr. William deB. MacNider, F.A.C.P., Chapel Hill, N. C.—"The Sick Individual as a Biological Problem."

The 4th Institute on Postgraduate Psychiatric Education for State Hospitals held under the auspices of the American Psychiatric Association was held at the Western State Hospital, Fort Steilacoom, Wash., September 1–13, 1941. Dr. Walter Freeman, F.A.C.P., Washington, D. C., and Drs. Frederick Lemere (Associate) and Edward D. Hoedemaker, F.A.C.P., Seattle, Wash., were among those who conducted the course, which included lectures and clinics.

Among the guest speakers at the 100th Annual Meeting of the State Medical Society of Wisconsin, held in Madison, September 10–12, 1941, were:

Dr. Henry W. F. Woltman, F.A.C.P., Rochester, Minn.—"Late Neurologic Manifestations in Cases of Injury";

Dr. James A. Evans, F.A.C.P., Boston, Mass.—"Cardiac Accidents and Their Management";

Dr. Philip S. Hench, F.A.C.P., Rochester, Minn.—"Classification and Management of Rheumatoid Disease";

Dr. John W. Towey, F.A.C.P., Powers, Mich.—"How Early Tuberculosis Can Be Detected in the Office."

Dr. Nathan B. Van Etten, F.A.C.P., New York, N. Y., spoke on "The Triumphs of Optimism" at the centennial dinner held during this meeting.

Dr. Carlo J. Tripoli, F.A.C.P., Assistant Professor of Medicine at Louisiana State University School of Medicine, New Orleans, has been appointed Director of the newly created Helis Institute for Medical Research. This Institute expects to establish various clinical and experimental divisions at medical schools and hospitals, the first of which has already been organized as the Center of Research of Hotel Dieu Hospital.

The Michigan State Medical Society held its 76th Annual Meeting at Grand Rapids, September 16–19, 1941. Among the speakers were:

Dr. Russell L. Cecil, F.A.C.P., New York, N. Y.—"Arthritis—A Curable Disease";

Dr. Francis E. Senear, F.A.C.P., Chicago, Ill.—"Serologic Aspects of Syphilis";

Dr. Lawrence Kolb, F.A.C.P., Washington, D. C.—"The Needs and Possibilities of Research in Mental Disease";

Dr. Charles E. Lyght, F.A.C.P., Northfield, Minn.—"Some Educational Aspects of Diagnosing Tuberculosis Early";

Dr. Virgil P. Sydenstricker, F.A.C.P., Augusta, Ga.—"Factors in Deficiency Disease";

Dr. Chester S. Keefer, F.A.C.P., Boston, Mass.—"Recent Advances in Chemotherapy of Infectious Diseases";

Dr. Arlie R. Barnes, F.A.C.P., Rochester, Minn.—"Problems in the Differential Diagnosis of Coronary Artery Disease";

Dr. Charles A. Doan, F.A.C.P., Columbus, Ohio—"Relationship of the Reticuloendothelial System to Cellular and Humoral Immunity."

Among the speakers at the 19th Annual Fall Clinical Conference of the Kansas City Southwest Clinical Society, held in Kansas City, Mo., October 6–9, 1941, were the following members of the College:

Dr. Sara M. Jordan, F.A.C.P., Boston, Mass.—"Medical Management of Peptic Ulcer";

Dr. Ernest Perry McCullagh, F.A.C.P., Cleveland, Ohio—"Clinical Use of Testicular Hormones";

Dr. John T. Murphy, F.A.C.P., Toledo, Ohio—"X-Ray Treatment of Cancer of the Skin";

Dr. Roy W. Scott, F.A.C.P., Cleveland, Ohio—"The Part Played by Age, Cardiac Hypertrophy and Coronary Arterial Change in Heart Failure."

Dr. Charles T. Stone, F.A.C.P., Galveston, Tex., spoke on "Newer Aspects of Pneumonia" and Dr. Oliver C. Melson, F.A.C.P., Little Rock, Ark., spoke on "Treatment of Hypertension" at the meeting of the Tri-State Medical Society (Louisiana, Texas and Arkansas), held in El Dorado, Ark., September 23–24, 1941.

Among the guest speakers at the 71st Annual Session of the Colorado State Medical Society held in Estes Park, September 17–20, 1941, were:

Dr. Louis E. Viko, F.A.C.P., Salt Lake City, Utah—"Evaluation of Chest Pain";

Dr. Elmer L. Sevringhaus, F.A.C.P., Madison, Wis.—"Pituitary Therapy in General Practice; Treatment of the Menopause."

The 1941 Scientific Assembly of the Medical Society of the District of Columbia was held in Washington, September 30–October 2, 1941. Among the speakers were:

Dr. Soma Weiss, F.A.C.P., Boston, Mass.—"Pre-eclamptic and Eclamptic Toxemia in Pregnancy";

Dr. Thomas Fitz-Hugh, Jr., F.A.C.P., Philadelphia, Pa.—"Differentiation of Anemias";

Dr. Oscar B. Hunter, F.A.C.P., Washington, D. C.—"Newer Laboratory Procedures in the Diagnosis of Obscure Fevers";

Dr. Wendell S. Muncie, F.A.C.P., Baltimore, Md.—"Why Are There so many Neurotics?";

Rear Admiral Ross T. McIntire, F.A.C.P., (MC) U. S. N.—"Aviation Medicine in the Navy";

Major General James C. Magee, F.A.C.P., (MC) U. S. A.—"Care and Evacuation of Battle Casualties in Modern War";

Lieut. Comdr. Lloyd R. Newhouser, F.A.C.P., (MC) U. S. N.—"Use of Blood Substitutes by the Armed Forces";

Col. Leonard G. Rowntree, F.A.C.P.—"Health of the Nation as Revealed by Selective Service."

Among the guest speakers at the 92nd Annual Session of the Indiana State Medical Association, held in Indianapolis, September 23–25, 1941, were:

Dr. Louis Hopewell Bauer, F.A.C.P., Hempstead, N. Y.—"Aviation Medicine";

Dr. James P. Leake, F.A.C.P., U. S. Public Health Service—"Poliomyelitis";

Dr. Ralph Pemberton, F.A.C.P., Philadelphia, Pa.—"Arthritis";

Dr. Russell L. Haden, F.A.C.P., Cleveland, Ohio—"More Common Blood Dyscrasias Seen by the General Practitioner";

Dr. Fred M. Smith, F.A.C.P., Iowa City, Iowa—"Management of the Patient with Coronary Disease."

Dr. James O. Ritchey, F.A.C.P., Indianapolis, was chairman of a panel discussion on "The Clinical Application of the Newer Laboratory Procedures as Pertains to the Man in General Practice."

Dr. Archibald H. Beard, F.A.C.P., and Dr. Samuel A. Weisman, F.A.C.P., have been promoted to Clinical Associate Professors of Medicine at the University of Minnesota Medical School, Minneapolis.

Under the presidency of Dr. Walter B. Martin, F.A.C.P., Norfolk, the Medical Society of Virginia held its annual meeting at Virginia Beach, October 6–8, 1941. Comdr. Waddie P. Jackson, (MC) U. S. N. R. (Associate), Norfolk, spoke on "The Airplane, a Possible Means of Transmission of Disease," and Dr. Louis Hamman, F.A.C.P., Baltimore, Md., conducted a clinical pathologic conference.

The Scientific Society of San Antonio (Texas) recently presented the Franklin Medal to Col. Charles F. Craig (MC) U. S. A., Retired, F.A.C.P., San Antonio, for distinguished work in science. Colonel Craig is the first recipient of this medal, which was donated by Colonel and Mrs. W. Lee Hart of San Antonio and named in honor of the late Dr. Thomas H. Franklin.

The Philadelphia County Medical Society held its inaugural meeting September 17, 1941. At this meeting Dr. Louis H. Clerf, F.A.C.P., was installed as President of the Society, succeeding Dr. Edward L. Bortz, F.A.C.P., College Governor for Eastern Pennsylvania.

Dr. Louis Faugeres Bishop, Jr. gave a talk on "The Senile Heart" at the Sixth Harlow Brooks Memorial Clinical Conference at the Sage Memorial Hospital, Ganado, Arizona, August 25, 1941. He also delivered the Commencement Address on "Harlow Brooks" to the graduating class of the Sage Memorial Hospital School.

Dr. Joseph H. Barach, Pittsburgh, Pa., addressed the Jefferson County Medical Society at Punxsatawny, Pa. on September 11, 1941. His subject was "Present Day Treatment of Diabetes and Its Complications."

Dr. Walter Reece Berryhill Elected Dean of the University of North Carolina School of Medicine

Announcement was made September 9 that Dr. Walter Reece Berryhill, F.A.C.P., had been elected Dean of the School of Medicine and Chairman of a newly-created division of medical sciences of the University of North Carolina, the election having been made by the Executive Committee of the Board of Trustees.

Dr. Berryhill graduated from Harvard Medical School in 1927, and had been acting dean of the School of Medicine of the University of North Carolina since the resignation a year ago of Dr. W. DeB. MacNider, F.A.C.P., who, after overseeing the construction of the school's new home, resigned to return to laboratory and classroom work. Dr. Berryhill is also to head the new division of medical sciences which will include the School of Medicine, the School of Public Health, the County Health Service and the University Health Service. It is said the purpose of the new division is to correlate and strengthen the various activities in the medical field at the University.

Dr. Berryhill is a native of Charlotte, North Carolina, where he was born in 1900. He attended the Charlotte schools and entered the University of North Carolina, receiving his A.B. degree in 1921. He distinguished himself as an undergraduate and was class president and head of the student council during his senior year. He returned to the University in 1923 and enrolled in the Medical School, but later transferred to Harvard Medical School from which he graduated in 1927. He served as intern and resident physician in Boston City Hospital and at Lakeside Hospital in Cleveland from 1927 to 1930, and from 1930 to 1933 was instructor in medicine and attending physician at Lakeside Hospital. He returned to the University of North Carolina in 1933 as university physician and rapidly advanced to associate professor in medicine, assistant dean and acting dean of the Medical School, culminating in his present appointment as Dean.

OBITUARIES

DR. ALLEN KRAMER KRAUSE

On May 12, 1941, after several years of serious illness, Dr. Allen Kramer Krause died in Providence, Rhode Island at the age of 60 years.

He was born in 1881 in Lebanon, Pennsylvania and was graduated from Brown University in 1901, receiving his A.M. degree from the same university in 1902. He received the degree of M.D. from Johns Hopkins University in 1907 and, except for a brief period during which he was Assistant Director of the Saranac Laboratory, subsequently was an active member of the Johns Hopkins Faculty for nearly 20 years, first as Instructor in Pathology, later as Associate Professor of Medicine, Director of the Kenneth Dows Tuberculosis Research Laboratories, Associate Physician, Johns Hopkins Hospital and Physician-in-Charge of the Phipps Tuberculosis Dispensary. When he left Baltimore in 1929 to take charge of the Desert Sanatorium in Tucson, Arizona, he was made Visiting Lecturer in Medicine at Johns Hopkins University. While he was in the south west, Stanford University appointed him (1929) Clinical Professor of Medicine and in 1932 the University of Southern California conferred the same honor upon him.

He was an active member of many scientific societies, too numerous to detail. He was an honorary member of the Harvey Society, the Interurban Clinical Club, the American Society of Clinical Investigation and the Los Angeles Clinical and Pathological Society.

During the first five years of its existence, that is, from 1917 to 1922, he was Managing Editor of the *American Review of Tuberculosis* and subsequently, Editor. He was Editor of the American Section of the British journal *Tubercle* and on the Editorial Board of a number of other important foreign medical journals. He was the author of articles on tuberculosis in the *Encyclopedia Britannica,* Nelson's *Loose Leaf System of Medicine,* Osler's *Modern Medicine,* Piersol's *Cyclopedia of Medicine* and Cecil's *Text-Book of Medicine.*

In 1931 he was the recipient of the Trudeau Medal of the National Tuberculosis Association. In American Men of Science he was " starred."

Allen Krause had a brilliant mind in a too frail body. Tuberculosis which troubled him early after graduation at Johns Hopkins never really laid him low. This brief illness seemed only to stimulate his interest in the historical, clinical, experimental and public health aspects of the disease. It led to his important studies on allergy and immunity, to his editorial opportunities, to his official positions in the Phipps Dispensary at Johns Hopkins and finally to his migration to the south west. It led to his voluminous writings and innumerable addresses all over the United States. He read everything and seemed to remember everything he read. He spoke with great fluency and assurance to both laymen and the medical profession.

Through his editorial efforts the *American Review of Tuberculosis* rapidly assumed and has maintained a leading place in its field. As Editor, Allen Krause had the opportunity which he generously utilized to encourage much experimental work in tuberculosis in American laboratories. In every city he had a host of devoted admirers, who flocked to hear his formal addresses and pursued him afterwards to his hotel room where he loved to "hold forth" until the small hours of the morning. The volume of work, editorial and other writing which he did was enormous. The rapidity with which he did it and its accuracy, clarity and fluency were phenomenal.

Tragedy tortured his last few years but the record of his brilliant life is unique in American medicine.

JAMES J. WARING, M.D., F.A.C.P.,
Governor for Colorado

DR. HENRY JOACHIM

Dr. Henry Joachim died at his residence in the Waldorf Astoria Towers in New York City, on August 18, 1941, of carcinoma of the cecum, having made his own diagnosis prior to the time of examination by his colleagues.

Dr. Joachim was born in Brooklyn, on April 16, 1883, and his professional activities were both in New York City and Brooklyn. He received his medical degree from Cornell University in 1904 and then had postgraduate study at the Allgemeine Krankenhaus, Vienna, and at the University of Prague, 1905–06–07. Following his return to the United States, he started his practice in Brooklyn and became an Associate in Medicine at the Brooklyn Jewish Hospital from 1911–1923. During this time he was made Instructor in Histology and Bacteriology at the Long Island Medical College and in 1918 he became the head of the department of Gastroenterology and Clinical Professor of Medicine, serving until 1931. During this time he was Attending in Medicine at St. Catherine's Hospital, 1916–1923; Chief in Medicine, Greenpoint Hospital 1918–1923; Attending in Medicine, Long Island College Hospital, 1918–1932. At the time of his death he was Director of Medicine, Cumberland Hospital; Chief of Medicine, Beth-Moses and Israel-Zion Hospitals, Jewish Sanitarium and Hospital for Chronic Diseases; Chief of Medicine, Sydenham Hospital, New York City. He was a member of the State Industrial Council and past president of the Medical Society of the County of Kings and the Brooklyn Academy of Medicine, Fellow of the New York Academy of Medicine, the American Medical Association, and a Fellow of the American College of Physicians since 1920. He was author of a host of published articles in leading medical journals, and of "Practical Diagnosis and Treatment" (Charles Thomas Company, 1940).

Dr. Joachim was an inspiring teacher and a keen diagnostician. It was for these reasons that his ward rounds and clinics always attracted a large audience. The outstanding traits of Dr. Joachim's character were his re-

markable encyclopedic memory, his scientific acumen, and, above all, his gentleness of character. He was highly respected and admired by all who had the privilege of contact with him.

C. F. TENNEY, M.D., F.A.C.P.,
Governor for Eastern New York

DR. ISADORE KAUFMAN

On August 11, 1941, medicine lost an active and interested member with the death of Dr. Isadore Kaufman.

Dr. Kaufman was born in Charlottesville, Virginia on April 21, 1882. He attended the University of Virginia, where he obtained his M.D. degree in 1904. He served a one year internship at Mt. Sinai Hospital in New York.

Being primarily interested in tuberculosis he gave generously of his time and efforts for that cause. Dr. Kaufman was Visiting Physician at White Haven Sanatorium from 1911 until the time of his death. He was also Medical Director of Kensington Dispensary for Tuberculosis since 1918 and Consultant in Pulmonary Diseases at the Abington Memorial Hospital.

For many years Dr. Kaufman was a lecturer in Physical Diagnosis and served as Head of the Department of Physical Diagnosis at the University of Pennsylvania School of Medicine. He was actively identified with the Henry Phipps Institute, having served as Clinician and Associate Clinical and Sociological Director in former years.

In addition to an already full schedule, Dr. Kaufman was the author of several published articles. He was a Fellow of The American College of Physicians since 1929; a member of The Philadelphia County Medical Society; a member of The National Tuberculosis Association; a Fellow of The American Medical Association, and a member of The Medical Society of The State of Pennsylvania.

With so much to contribute to the medical profession, and with a fine personality, Dr. Kaufman was held in high esteem by his colleagues and friends. It is therefore with deep regret that we write of his death.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. WILLIAM BERNARD KINLAW

Dr. William Bernard Kinlaw of Rocky Mount, N. C., was killed on July 24, 1941, in an automobile accident. He was born July 17, 1896, the son of Mr. and Mrs. H. R. Kinlaw of Rocky Mount.

After graduation from the high school of his native city, he attended the University of North Carolina, and graduated in medicine from the University of Pennsylvania in 1920. After two years' internship in the Episcopal Hospital of Philadelphia, he returned to his home city, where he spent a year

in general practice, after which he was associated in 1923–24 with Dr. P. P. McCain of the State Sanatorium. He then decided to devote himself entirely to internal medicine, and became attending physician to the Park View Hospital of Rocky Mount, and later the Memorial Hospital of Kinston. In 1939 and 1940 he practiced in Binghamton and Elmira, N. Y., returning to Rocky Mount in January, 1941.

His published material showed his more intense interest in pulmonary and cardiac conditions, though his bibliography includes such conditions as reports on Brill's disease, post vaccinal encephalitis, and effort syndrome.

He was a member of his local and state medical societies, of the Seaboard Medical Society, the Tri-State Medical Society, the American Medical Association, and became a Fellow of the American College of Physicians in 1929.

In 1923 he married Miss Dorothy Wisner of Philadelphia, Pa., who, with one son, W. B. Kinlaw, Jr., survives.

Dr. Kinlaw was a man of exceptionally attractive personality and great charm; his untoward death at the age of forty-five leaves a void in the affections of a great many of the profession who were privileged to know him well.

CHARLES H. COCKE, M.D., F.A.C.P.,
Governor for North Carolina

DR. WILLIAM HENRY WILSON

Dr. William Henry Wilson died at his home in Joliet, Ill., on May 15, 1941, at the age of seventy-four. Death resulted from cerebral thrombosis. Dr. Wilson was born near Brockville, Ont., Canada, on October 26, 1866. As a boy of seven he moved with his family to Benton County, Iowa. In 1893 he graduated from the University of Michigan. In common with many other ambitious young men, he began his first work as a teacher in the high school at Fort Smith, Ark., in the same year. In 1898 he received his medical degree from the Hahneman College at Chicago, Ill.

During the course of his long attachment to Hahnemann College, Dr. Wilson served as pathologist from 1900–1923, and from 1919–1923 he was registrar. In 1923, with the termination of the Hahnemann Medical College as an active teaching center, he moved to Joliet, and for the next 15 years he was pathologist at the Silver Cross Hospital. From 1903–1904 he was pathologist at Cook County Hospital.

Dr. Wilson was a Fellow (1923) of the American College of Physicians, a member of the American Medical Association, the American Society of Clinical Pathologists, the American Association for the Study of Neoplastic Diseases and the Will County Medical Society. He was a Mason, a Shriner, an active member of the Rotary Club in Joliet, a member of the alumni chapter of Sigma Alpha Epsilon and Phi Rho Epsilon. He was formerly vice-chairman of the consulting committee of the Chicago Department of

Health and a member of the Medical Reserve Corps of the United States Army. He is survived by his widow and two daughters.

Dr. Wilson was interested in nature study and in geology. He became particularly familiar with the interesting geological features around Joliet and Will County. He was an active participant in the efforts to extend the forest preserve system of Will County. Dr. Wilson was always deeply interested in opera and was recognized as an authority. At all times those who knew him recognized in him an educated physician and gentleman, whose alertness and general knowledge made him an interesting companion and friend.

LeRoy H. Sloan, M.D., F.A.C.P.,
Governor for Northern Illinois

DR. WILLIAM HURLEY STRIETMANN

Dr. William Hurley Strietmann, F.A.C.P., of Oakland, California, died on July 14, 1941. Death came suddenly while he was at his office, and was due to coronary artery disease.

Dr. Strietmann was born in Cincinnati, Ohio, November 8, 1880. He graduated from the University of Cincinnati College of Medicine in 1905 and went abroad for postgraduate work in Vienna from 1906 to 1907. He was appointed Instructor in Bacteriology at his Alma Mater in 1907. From 1908 to 1911 he was assistant in Physiology. In 1912 he was appointed Professor of Physiology at the Oakland College of Medicine, Oakland, California, and in 1916 he was made Associate Professor of Medicine. For several years he was Chief of the Medical Service at the Alameda County Hospital. He was a member of the Alameda County Institutions Commission, a member and past president of the Alameda County Medical Society; also member and past vice-president of the California State Medical Association. He was a Fellow of the American Medical Association and a Fellow of the American College of Physicians since 1917.

Dr. Strietmann was one of the first in Oakland to confine himself to Internal Medicine. He had a large consulting practice, but gave freely of his time and energy to the Alameda Institutions Commission and to the Alameda County Hospital, as physician-in-chief.

Two daughters and a son survive, but Mrs. Strietmann passed away about one year ago.

Dr. Strietmann's work is finished, but his influence will be felt among his patients and fellow physicians for long into the future.

Ernest H. Falconer, M.D., F.A.C.P.,
Governor for Northern California

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FAT METABOLISM IN DIABETES MELLITUS*

By WILLIAM C. STADIE, M.D., *Philadelphia, Pennsylvania*

THE enormous amount of research on the abnormal metabolic processes of diabetes mellitus since the time of v. Mehring and Minkowski has failed to bring unity of conviction to students of the disease. We find today, as in earlier times, two opposing hypotheses still striving for supremacy. These two hypotheses may be briefly stated as follows:

I. The under-utilization hypothesis states that the major defect in the intermediary metabolism of the diabetic is the inability of the tissues to oxidize sufficient carbohydrate for normal metabolic needs. In consequence, ingested carbohydrate and that derived from protein is excreted.

II. The over-production hypothesis postulates that the diabetic has no essential impairment of carbohydrate utilization in the periphery provided compensatory hyperglycemia is maintained. The primary defect lies in the liver which in diabetes produces an excess of glucose from fatty acids as well as protein.

TABLE I

Current Theories of the Diabetic Defect

I. Under-utilization:	The peripheral tissues, without insulin, cannot oxidize carbohydrate
II. Over-production:	The liver, without insulin, converts an excess of fatty acids to glucose

No matter which of these hypotheses is the true one, the complete diabetic animal is in a bad way. According to the under-utilization hypothesis, he is losing all of the energy derivable from carbohydrate, and about 50 to 60 per cent of that from protein. Hence, he is forced to fall back upon fat as the chief source of his energy requirements. According to the over-production hypothesis, the diabetic is pouring into the urine large amounts of fat in the form of sugar. In either case the question of fat metabolism becomes the paramount issue and it becomes imperative, therefore, to examine the hypo-

* Read at the Boston meeting of the American College of Physicians April 21, 1941.
From the Department of Research Medicine, University of Pennsylvania.

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theses of fat metabolism which grew up simultaneously with the development of these two hypotheses concerning the metabolic defect.

There is abundant evidence that a considerable fraction of the total fat metabolism is initiated in the liver. Differences of opinion arose as to the mechanisms of this hepatic fat oxidation and split the diabetic camp into two. The contending hypotheses are summarized in table 2. According to the

TABLE II

Contending Hypotheses Concerning the Preliminary Oxidation of Fatty Acids in the Liver

II–A. Fatty acids oxidized to ketone bodies + acetic acid.
II–B. Fatty acids oxidized to ketone bodies + glucose.
II–C. Fatty acids oxidized to ketone bodies only.

first of these, fats are preliminarily oxidized in the liver to ketone bodies plus a two-carbon compound, i.e., acetic acid. In the normal subject these are completely oxidized in the periphery, but in the diabetic the oxidation of the ketones is blocked. This represents the position of the under-utilization hypothesis.

The second hypothesis states that the fats are initially converted by the liver to glucose as well as ketone bodies. Both are equally well oxidized in the periphery by both normals and diabetics. This represents the position of the overproduction hypothesis.

The third hypothesis states that fats are completely converted in the liver to ketone bodies only. These are freely utilized by the peripheral tissues of the diabetic. This position represents, indeed, a new departure and is the one for which experimental evidence will be given.

Several influences converged to throw the first of these hypotheses into the limelight and obscure the others. These were: First, the ascendency of the under-utilization school led by Lusk; second, the strong position of the Knoop hypothesis of successive beta oxidation of fatty acids so strongly advocated by Dakin and Embden; and third, the development by Woodyatt and Shaffer of the hypothesis of the obligatory coupling of ketone oxidation with carbohydrate oxidation. It is necessary to examine these hypotheses closely since they are intimately concerned with the problem of the metabolic defect in diabetes.

TABLE III

Current Hypotheses of Fat Metabolism in the Diabetic

I. Knoop hypothesis of successive beta oxidation.
Long carbon chains of fatty acids oxidized two carbons at a time with formation of acetic acid + one ketone molecule per molecule of fatty acid.
E.g. Palmitic + 6.5 O_2 = 1 ketone + 6 acetic.
II. Ketones oxidized only by obligatory coupling with carbohydrate oxidation.
III. Fat converted to carbohydrate by liver.

According to the successive beta oxidation hypothesis, the oxidation of the long naturally occurring even numbered fatty acid chains containing 16 or more carbon atoms would proceed as follows: Beta oxidation would split off from the fatty acid molecule, one acetic acid leaving a residual fatty acid

shorter by two carbons. This mode of oxidation would continue so that each fatty acid would be degraded through a succession of fatty acids each shorter by two carbons than its immediate precursor. Finally, there would result one molecule of acetoacetic acid or beta oxybutyric acid, i.e., the ketone bodies. For every molecule of fatty acid oxidized only one molecule of ketone would be formed. The residual ketones could be oxidized only by one mechanism, namely by the simultaneous oxidation of a definite amount of carbohydrate defined by the ketogenic-antiketogenic ratio. In the diabetic, since there was no carbohydrate oxidation, the ketones accumulate as toxic or useless by-products of fat oxidation which are excreted in toto.

This combination of hypotheses was eagerly accepted by the under-utilization school. For it made it possible to explain how the complete diabetic who, losing 70 to 80 per cent of the energy from protein and 100 per cent of that from carbohydrate, could still exist. There was the 50 per cent of the original energy of the fat in the form of acetic acid. Moreover, the formation of this easily oxidizable and readily diffusible substance avoided the necessity of postulating the formation of carbohydrate from fat. And finally, the discovery of the ketogenic-antiketogenic ratio afforded a ready explanation, which appeared quantitative, of the marked influence of carbohydrate upon urinary ketone excretion.

The position of the over-production school was less definite as to the chemical reactions occurring during the oxidation of fatty acids in the liver. Much evidence, however, was marshalled to show that glucose was an end product of this oxidation, but this evidence brought little conviction to the under-utilizationists. Indeed, Lusk, the chief exponent of the under-utilization school in this country, characterized the possibility of the conversion of fat to carbohydrate as a " figment of the imagination " which should be relegated to " the realm of scientific superstition." However, the critical experiment which would decide the issue one way or another still remained to be done.

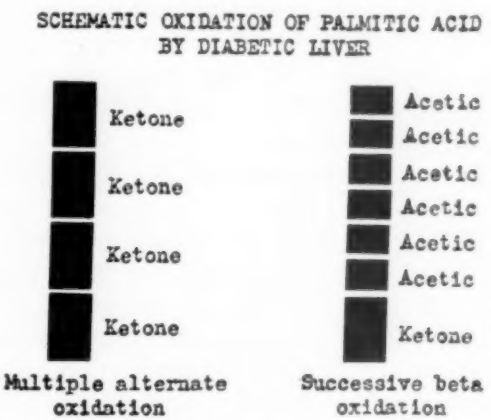

FIG. 1.

The English clinician Hurtley in 1916 rejected the Knoop hypothesis mainly upon theoretical grounds and in its place proposed the multiple alternate oxidation hypothesis. This hypothesis, which has slowly accumulated evidence, is shown in a schematic way in figure 1 where it is contrasted with the Knoop hypothesis. The hypothesis postulates that there is a multiple oxidation at alternate carbon atoms along the entire length of the fatty acid chain. In consequence the entire fatty acid molecule is disrupted completely into ketone bodies only. In contrast, the Knoop hypothesis supposes a step by step splitting off of acetic acid molecules leaving a residue of one molecule of ketone. The chemical consequences of the multiple alternate oxidation hypothesis for the oxidation of a typical acid such as palmitic are as follows: (1) For the production of one molecule of ketone there should be required by the liver 1¼ molecule of oxygen instead of 6½; (2) for every molecule of fatty acid oxidized there should appear four molecules of ketones instead of one; and finally (3) the oxidation of one molecule of fatty acid should yield no acetic acid whatever instead of six molecules.

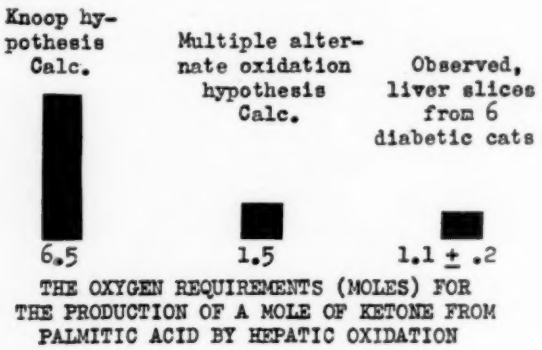
Knoop hypothesis Calc.
Multiple alternate oxidation hypothesis Calc.
Observed, liver slices from 6 diabetic cats
6.5
1.5
1.1 ± .2
THE OXYGEN REQUIREMENTS (MOLES) FOR THE PRODUCTION OF A MOLE OF KETONE FROM PALMITIC ACID BY HEPATIC OXIDATION

FIG. 2.

Now if a depancreatized cat with full blown ketosis is taken, the answer to this problem should be found in the fat metabolism of the liver. In association with Dr. Francis D. W. Lukens, Director of the Cox Institute, and Dr. John A. Zapp, Jr., of the Department of Research Medicine, experiments were done, part of which are reported here. In general the method was as follows: two or three days after removal of the pancreas, the animal was sacrificed and liver slices were prepared and equilibrated in vitro in suitable buffers together with oxygen. Using appropriate analytical methods certain metabolic processes occurring in the liver could be followed.

In the first type of experiment shown in the slide we determined the moles of oxygen required by the liver to form one molecule of ketone. The Knoop hypothesis requires 6.5; the multiple alternate oxidation hypothesis requires 1.5. We found a mean value in six diabetic cats of 1.1. This ratio is not significantly different from that demanded by the multiple alter-

nate oxidation hypothesis but quite significantly different from that of the Knoop hypothesis.

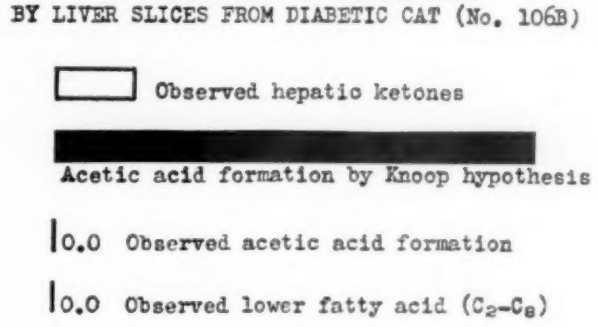
NON-FORMATION OF ACETIC ACID
BY LIVER SLICES FROM DIABETIC CAT (No. 106B)
Observed hepatic ketones
Acetic acid formation by Knoop hypothesis
0.0 Observed acetic acid formation
0.0 Observed lower fatty acid (C2-C8)

FIG. 3.

In the second type of experiment we looked for the possible formation of acetic acid in the slice from livers of diabetic cats. These livers were oxidizing fatty acids in a lively fashion as shown by abundant ketone formation. According to the Knoop hypothesis the large amounts shown on the slide should have been found, yet we found no acetic acid formation whatever. We also looked for the lower fatty acids containing one to eight carbons supposedly formed by successive beta oxidation but could find none.

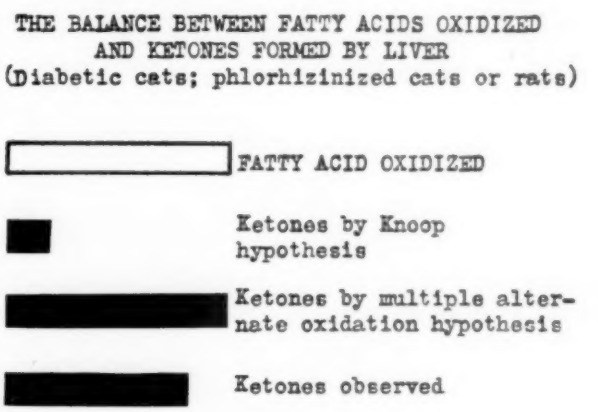
THE BALANCE BETWEEN FATTY ACIDS OXIDIZED
AND KETONES FORMED BY LIVER
(Diabetic cats; phlorhizinized cats or rats)
FATTY ACID OXIDIZED
Ketones by Knoop hypothesis
Ketones by multiple alternate oxidation hypothesis
Ketones observed

FIG. 4.

In the third type of experiment we measured the fatty acid balance of liver slices from diabetic cats. The Knoop hypothesis says that one fourth of the fatty acid oxidized should appear as ketones; the multiple alternate oxidation hypothesis says that all of the fatty acid oxidized should be converted into ketones. We found by experiment with eight diabetic or phlorizinized cats or rats that ketone formation practically accounted for all of the

fatty acid oxidized, a result anticipated from the multiple alternate oxidation hypothesis.

The summation of the evidence in these experiments brought us to the conviction that the Knoop hypothesis of successive beta oxidation as an explanation for the major part of the fatty acid oxidation occurring in the liver must be abandoned and replaced by the multiple alternate oxidation hypothesis.

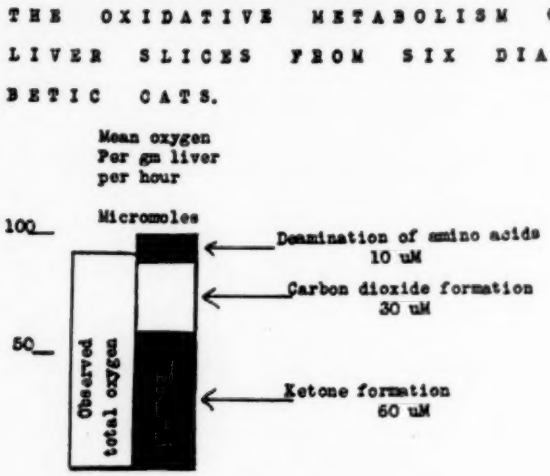
THE OXIDATIVE METABOLISM OF LIVER SLICES FROM SIX DIABETIC CATS.
Mean oxygen Per gm liver per hour
Micromoles
100
50
Observed total oxygen
Deamination of amino acids 10 uM
Carbon dioxide formation 30 uM
Ketone formation 60 uM

FIG. 5.

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A moment's reflection should show that these experiments enable us to write the reaction for the oxidation of fatty acids by the liver of the diabetic cats. We find that it is not necessary to include glucose in that reaction. However, two other types of evidence were obtained on this point. Firstly, an oxidative balance of the liver slices from diabetic cats can be obtained. Three known oxidative processes were independently measured and the oxygen required for each calculated. They are shown in figure 5 and are: (1) formation of urea by deamination of amino acids, (2) formation of carbon dioxide, and (3) formation of ketone bodies. The sum of these three was found, in the case of six diabetic cats, to be not significantly different from the total observed oxygen uptake. In other words, there was no oxygen available for any other oxidative process. But the conversion of fats to glucose requires oxygen, and these same cats excreted one to four hours before the experiment amounts of glucose which if it came from fats would have required all or more oxygen utilization than that actually observed. The experiment, however, shows that there was, in the metabolism of the liver, no oxygen whatever available for this synthesis; hence, we are again forced to exclude the possibility of glucose formation from fats in the liver of the diabetic cat.

In the second type of experiment bearing on this point, we constructed a balance sheet of the actual new formation of carbohydrates by the diabetic liver slice. Our data allowed us to calculate amounts of glucose which might arise from protein, lactic acid, or glycerol. Within the limits of error we found no unaccounted for new carbohydrate which could be attributed to fat. In contrast to our inability to demonstrate formation of glucose from fat was our experience with a known precursor of carbohydrate. For example, these same liver preparations in the presence of lactic acid formed new carbohydrate up to 10 mg. per gm. per two hours, an amount sufficient to account for a large fraction of the glucose (75 per cent) actually excreted by the cat in a preliminary period of observation.

These experiments on depancreatized cats reënforced by new and old evidence in the literature both in experimental diabetes and diabetes mellitus, have brought us the conviction that the hypothesis which maintains that there is conversion of fatty acids to glucose in the liver is untenable.

Apparently then, the complete diabetic is producing nothing but ketones by oxidation of fats in the liver, and he would certainly be in a sad state if he could not utilize these ketones peripherally, for then fats would be gone, carbohydrates gone, and protein almost gone, and he would have nothing to fall back upon for his energy requirements. The demonstration that the diabetic could utilize ketones peripherally became of prime importance. In five ways (two are presented here) we showed that the diabetic does, in fact, utilize them.

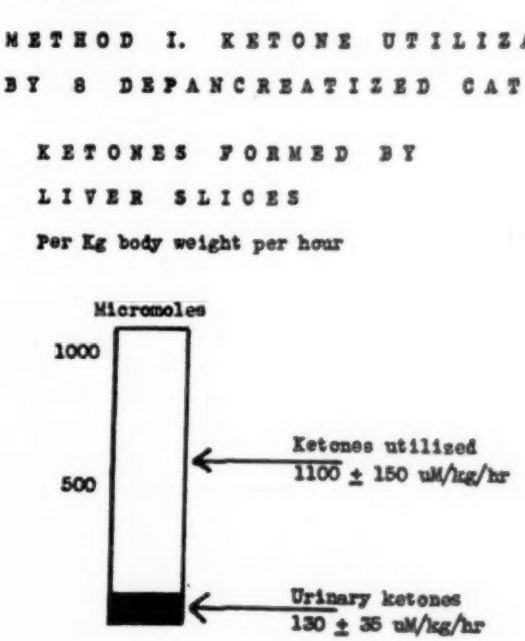

FIG. 6.

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First we measured the urinary ketone excretion in the diabetic cat. Then the animal was sacrificed and ketogenesis by the liver slices measured. In all cases the total ketone formation by the liver was greatly in excess of the urinary ketone excretion. The difference can only represent the ketone body utilization by the peripheral tissues, chiefly muscle, of the intact diabetic cat. The value found is equivalent to 1.9 gm. of fat/kg./day.

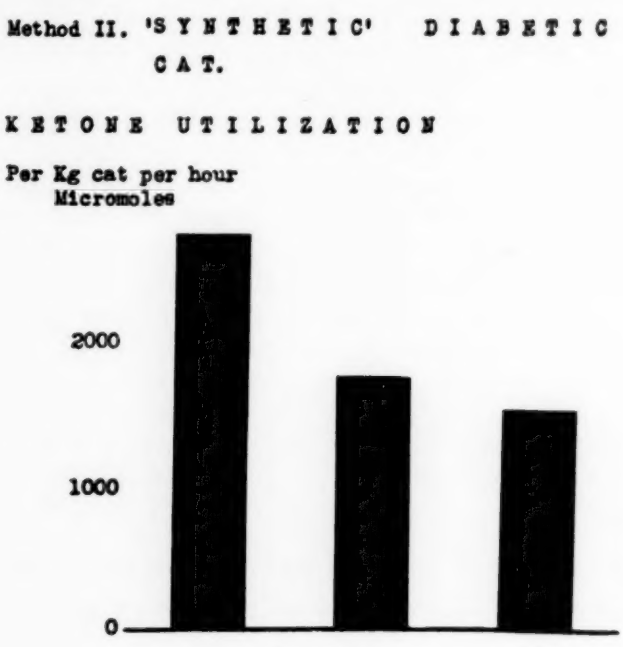

FIG. 7.

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In the second method we again showed that the muscle tissue from diabetic cats utilized ketone bodies. In this case the diabetic muscle tissue was equilibrated together with a slice of the liver from the same cat. By this device the muscle tissue was continuously supplied with ketone bodies formed by the diabetic liver and the conditions in the living cat simulated. By the use of appropriate controls it was possible to calculate the ketone utilization which was found to be, in terms of fat, equal to 3.7 gm./kg./day.

In the third method, we showed more directly that the muscle tissue of the diabetic animal utilized ketones. Muscle tissue was equilibrated with known amounts of acetoacetic acid. In all cases the ketone was diminished after equilibration with the muscle, and the calculated rate of utilization was equivalent to 1.6 mg. of fat/kg./day.

These results obtained by the use of surviving tissue equilibrated in vitro were corroborated in the intact diabetic cat by the determination of the ketone difference between the portal and the hepatic blood. The outgoing

hepatic concentration was always found to be higher than the ingoing portal concentration. Calculations using estimated hepatic blood flows showed that hepatic ketogenesis was greatly in excess of urinary ketone excretion. In other words there was, as with the slices, considerable ketone utilization by the peripheral tissues of the diabetic cat, which in the mean was found to be equivalent to 2.3 gm. of fat/kg./day.

TABLE IV

Ketone Utilization by Depancreatized Cats

Method No.	Number of cats	Ketone utilization, per Kg. cat per hour
		Micromoles
I. Ketone formation by liver slices minus ketone excretion	8	1100±150
II. "Synthetic" cat	3	2070±265
III. Acetoacetic acid equilibrated with muscle	5	915±265
IV. From portal vein-hepatic vein ketone conc. and blood flow	3	1265±260
Mean	19	1340±260

All these results are in accord with one another and with other data in the literature. The situation seems now to be fairly clear. It appears highly reasonable to exclude the over-production hypothesis as an explanation of the diabetic defect and adhere to the under-utilization hypothesis. The diabetic in calling for reserve energy from fat can muster a considerable fraction of his needs by oxidizing fatty acids to ketones in the liver. These ketones are freely used in the periphery without insulin and without the necessity of simultaneous coupling with the oxidation of carbohydrates.

But there still remained in the ketogenic-antiketogenic ratio a remnant of the obligatory coupling hypothesis, that is, the hypothesis epitomized by the aphorism " the fats burn in the flame of the carbohydrates." This ratio has been established in human cases of diabetes and it became necessary to reëxamine the assumptions and calculations upon which it had been based.

The assumptions were clearly stated by Shaffer, and I quote: "The hypothesis states that antiketogenesis in the human subject is based upon a ketolytic reaction in the body between acetoacetic acid, the first formed of the acetone bodies, and a derivative of glucose (or other antiketogenic substances), the compound being further oxidized, but that failing to react with ketolytic substance, acetoacetic acid is resistant to oxidation, accumulates, and is . . . excreted. . . . The fact that one finds at the threshold of ketosis an approximately constant ratio between the number of molecules of the precursors of acetoacetic acid and of glucose in the metabolic mixture, must mean that further oxidation of acetoacetic acid constantly taking place under normal conditions is accomplished through a chemical reaction with a derivative of glucose. . . ."

Fortunately, there are in the literature a series of classical cases reported before the advent of insulin when severe ketosis was of necessity a frequent accompaniment of the disease. The data include calorimetric measurements of the metabolic mixture of protein, fats, and carbohydrates together with total ketone excretion. Hence it is possible to calculate the total carbohydrate or so-called antiketones oxidized, the total fat catabolized, and the total fat utilized. The best way to examine the data is to put the hypothesis in the form of an equation. Curiously enough this never was done. Figure 8 shows the data in the case of Bessie B. reported by Wilder, Boothby and

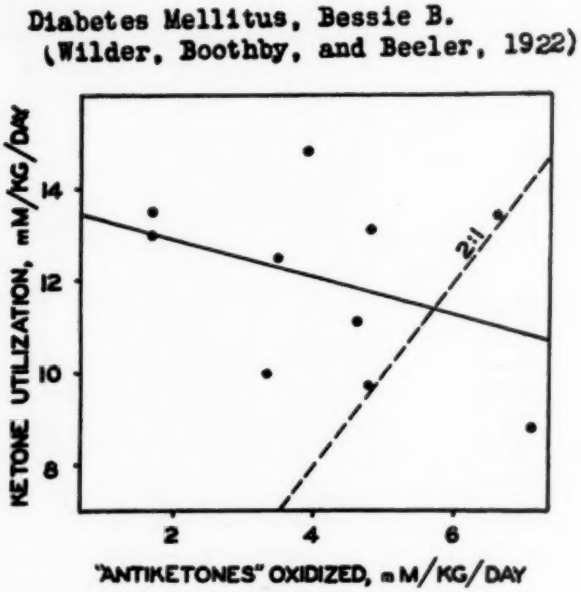

FIG. 8.

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Beeler. The ordinate shows the fat utilization expressed in terms of mM of ketones. The abscissa shows the mM of antiketones oxidized. The hypothesis is expressed by the dashed line for a ketone-antiketone ratio of 2 : 1. But the true line calculated from the data runs in the opposite direction with no relation whatever to the theory. Moreover, it is important to note that the intercept constant when antiketones oxidized were zero is about 14 mM, equivalent to about 1 gm. of fat/kg./day. This value is greatly different from zero which it should be according to the theory. That is to say, Bessie B. was utilizing ketones even in the practically complete absence of carbohydrate oxidation, a conclusion in conformity with our experiments with diabetic cats and opposed to the obligatory coupling hypothesis.

One more representative case is shown, that of Cyril K., reported by Gephart, Aub, DuBois and Lusk. Of all the cases in this group the dotted

line for the theory shows the best agreement to the "eye." But this agreement is entirely specious when the statistical analysis is considered, for the true line shows a slope of .7 instead of 2 and moreover when antiketones are zero, that is when no carbohydrate whatever was being oxidized, Cyril K. was completely oxidizing 90 gm. of fat per day without ketonuria and without simultaneous oxidation of carbohydrate, a conclusion in conformity with our experiments on diabetic cats.

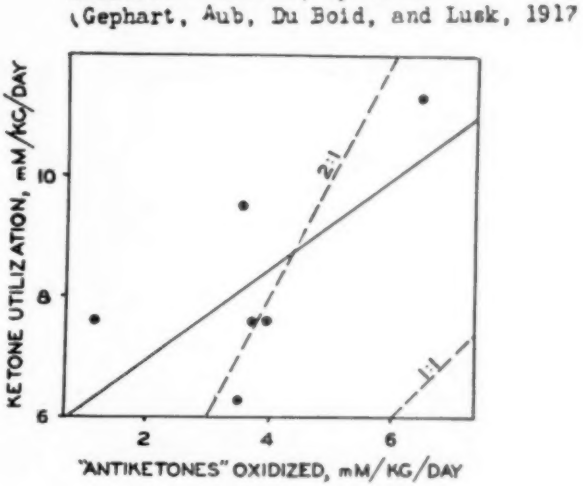

FIG. 9.

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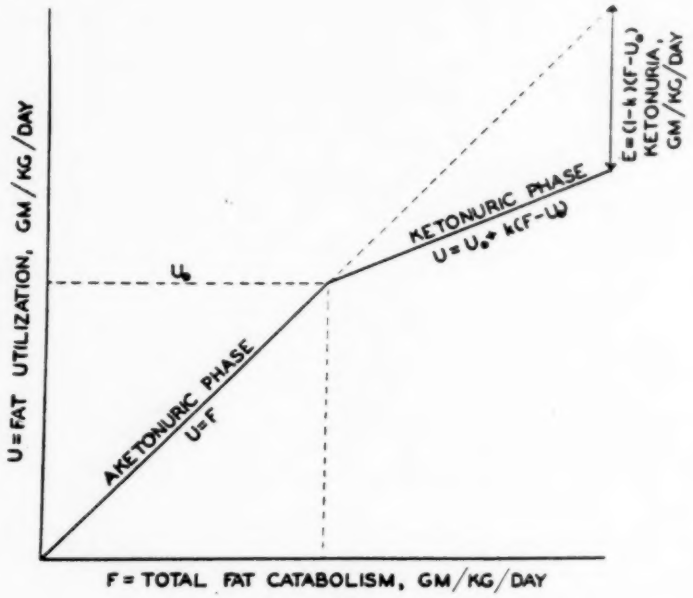
Four other cases for which data were available showed the same as did these two illustrative cases, and it seemed to us that the last remnant of the obligatory coupling hypothesis as expressed in the ketogenic-antiketogenic ratio had vanished. It remained, therefore, to formulate an hypothesis of fat metabolism in diabetes mellitus which would be in conformity with these observations. The following appears to fulfill these requirements:

Up to a certain level all fat catabolized is completely utilized; hence, there is no ketonuria. Beyond this level all fat catabolized is not completely utilized; hence, part of the fat catabolized is excreted in the form of ketone bodies.

The relation of carbohydrate to fat metabolism is a simple inverse one: The greater the carbohydrate utilized, the less is the fat metabolism; that is, carbohydrates spare fats.

The diagram in figure 10 shows the implications of this hypothesis. The abscissa shows F the total gm./kg./day of fat catabolized, that is, fat poured into the stream of intermediary metabolism. The ordinate shows U, the total fat utilized, that is the amount of fat which is completely oxidized.

There are two phases in the metabolism of fat. The first is the aketonuric phase; the second is the ketonuric phase. Starting at zero and increasing the amount of fat catabolized, we pass through the aketonuric phase along the line marked U = F. Here all fat in the metabolic stream is completely utilized and there is no ketonuria. But at any given state of activity, the ability of the diabetic to mobilize exactly that amount of fat which can be completely utilized appears to be limited. This upper limit I call the maximal aketonuric fat utilization indicated by U, the horizontal line on the



SCHEMATIC REPRESENTATION OF FAT METABOLISM IN DIABETES MELLITUS

FIG. 10.

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diagram. If the call for fat calories exceeds this aketonuric level, it is answered in the following way. Extra fat is catabolized above and beyond this level, but only a part of this extra fat is completely utilized. This is shown by the bending of the line marked "ketonuric phase" away from the extended dotted line which would represent complete utilization. The difference in fat between these two lines, indicated by the double arrow on the right, is not utilized, and hence is excreted in the form of the ketones. In other words, the diabetic can only increase his energy from fat above the basal aketonuric level by paying for it with base combined with urinary ketone acids, at the risk of acidosis.

This hypothesis can easily be tested by applying the data of diabetic cases in the ketonuric phase. The first illustrative case is No. 740 of Joslin. The data represent, as before, the metabolic mixture determined by calorimetric

methods. In the diagram on the left the abscissa shows the total fat catabolized expressed in micromoles of ketones per kg. per hour. The ordinate shows the total fat completely utilized. The observations for a series of days in this case fall about the straight line as expected from the hypothesis. At 1200 catabolism and utilization are equal, hence there was no ketonuria; 1200 micromoles, equivalent to 2 gm. of fat/kg./day, was the aketonuric fat utilization in this case. When this level was exceeded, for example at 1800 micromoles, only 1600 were utilized. In other words about $\frac{1}{9}$ of the total fat catabolized was excreted as ketone bodies. The diagram on the right of figure 11 shows the same data plotted according to the ketogenic-anti-

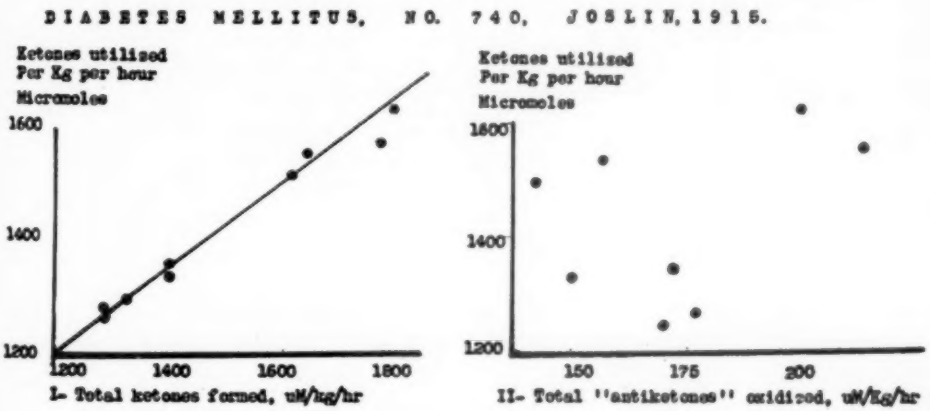

FIG. 11.

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ketogenic hypothesis. It is obvious, as was shown before, that there is no relation between ketone utilization and the oxidation of the so-called anti-ketones.

By way of illustrating the fact that the hypothesis could just as well have been framed in terms of urinary ketone excretion I show the data in one case, that of Cyril K. The total fat mobilized is shown along the abscissa, and the urinary ketones are shown on the ordinate in the same units. The data fall about a straight line as expected. Note that when the urinary ketones are zero, fat utilization is 1500 uM/kg./hr. equivalent to 150 gm. of fat per day. This was Cyril K.'s basal aketonuric fat utilization value. Note further that when he increased his fat catabolism by 1000 uM he excreted about 600 out of this extra 1000. In other words, Cyril K. could use only about 40 per cent of the fat he catabolized above his basal aketonuric level.

All the cases for which there were data available in the literature showed the same relations as those shown. The analysis of these cases is shown in table 5. There are 12 cases altogether, all from different clinics but studied by essentially the same methods. In the third column is shown the basal aketonuric fat utilization value. With the exception of Mosenthal and

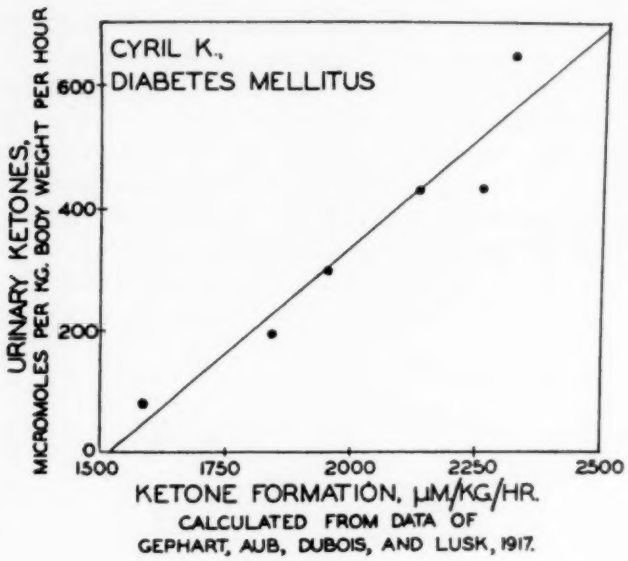

FIG. 12.

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Lewis' case, the one case with infection and fever, the values for the aketonuric fat utilization value are all concordant. The mean value is equivalent to 2.5 gm. of fat/kg./day.

We take these results, which are in agreement with our experiments with diabetic cats, to constitute evidence supporting the hypothesis of fat metabolism in the diabetic here advanced.

TABLE V

Summary of Maximal Basal Aketonuric Fat Utilization in Cases of Diabetes Mellitus

Case	Reference	Maximal aketonuric fat utilization in equivalents of ketone bodies	Coefficient of excess fat utilization
		mM. per kg. per day	
Group I			
Cyril K.	Gephart, Aub, DuBois and Lusk (25)	35	+0.41
Bessie B.	Wilder, Boothby and Beeler (24)	34	+0.75
Kramer	Shaffer (22)	35	+0.28
740	Joslin (23)	28	+0.75
E. W.	Mosenthal and Lewis (27)	(47)*	−0.38
Jervis B.	Richardson and Ladd (26)	23	+0.84
Group II			
Ray H	Richardson and Ladd (26)	37	
Chris. Q.	Richardson and Ladd (26)	26	
Harold J.	Richardson and Ladd (26)	37	
George H.	Richardson and Ladd (26)	37	
Frank B.	Richardson and Ladd (26)	37	
K. A.	McClelland, Spencer, and Falk (28)	40	
	Mean (11 cases)	34±1.6 (S. E. of mean)	
	Equivalent in grams of fat	2.5±0.12	

* Excluded from basal mean on account of fever (102° F.).

The results of these experiments, together with related evidence in the literature, may be summed up as follows:

1. The diabetic who by reason of insulin lack is unable to utilize carbohydrates to the full measure of his metabolic needs, must fall back on fat for his energy requirements. Part of this need is met by the initiation and completion of fat oxidation in the muscles themselves. However, a considerable fraction estimated as ⅓ to ½ of the total caloric needs from fat is obtained by a preliminary oxidation of fats in the liver to ketone bodies only. Neither acetic acid nor glucose is formed by this oxidation. These hepatic ketone bodies are freely utilized for energy by the periphery without insulin and without the necessity of simultaneous carbohydrate oxidation. This reserve mechanism, however, appears to be incapable of fine regulation so that when the demand for fat calories exceeds a certain level, approximately 2.5 gm. of fat/kg./day for the resting state, ketone bodies in excess of needs are formed by the liver. The excess is excreted as ketones in the urine. If this excessive fat catabolism continues unchecked, ketosis and coma follow.

STUDIES OF THE FACTORS CONCERNED IN EDEMA FORMATION. II. THE HYDROSTATIC PRESSURE IN THE CAPILLARIES DURING EDEMA FORMATION IN RIGHT HEART FAILURE *

By GEORGE FAHR, M.D., and IRVING ERSHLER, M.D.,
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ONE often hears eminent clinicians state that cardiac edema is due to increased permeability of the walls of the capillaries consequent to oxygen deficiency or to stasis within these vessels. This, despite the fact that not infrequently the oxygen content of the venous blood from the edematous limb shows no very marked reduction; and marked reduction in oxygen content of the venous blood as in the cyanotic group of congenital heart disease, may not be associated with edema throughout a period of many years. Even more marked degrees of oxygen reduction are far from the anoxemia levels at which capillary permeability shows a qualitative change. The degree of anoxemia that Landis[1] has shown to be necessary to produce a conspicuous change in the permeability of the wall of the capillaries of the frog mesentery is probably never found in heart failure except just before death. Moreover, our investigations of the edema fluid obtained from the legs in right heart failure lend no support to the idea of increased capillary permeability. This fluid contains the salts of the plasma in almost the same concentration as in the plasma itself, the slight difference being explained by the so-called Gibbs-Donnan equilibrium. The protein content of cardiac edema fluid varies from 0.1 to 0.5 per cent which is nearly the same as the content of edema fluid in nephritis and nephrosis.† This moderate amount of protein content in the edema fluid which corresponds to colloid osmotic pressures of from 0.25 to 1.5 mm. Hg is such that it alone could not possibly explain edema formation.

Let us see what light can be shed on the problem of edema formation in right heart failure by a review of our knowledge of fluid exchange between the blood plasma in the capillaries and the surrounding tissue spaces. All physiologists now agree with Starling [2] that the capillary is the site of fluid exchange between the blood plasma and the tissue spaces and that the capillary wall is a fairly perfect ultrafilter in most parts of the body, certainly in the subcutaneous areas where most of the edema accumulates. This ultrafilter allows water and salts to pass freely across it but prevents the passage of the plasma proteins. These capillary ultrafilter membranes are not completely

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From the Department of Medicine, University of Minnesota and Minneapolis General Hospital.
† These data will be published in the near future in a paper by Fahr and Koschnitzke.

perfect but in certain areas of the wall they allow plasma proteins to pass through them so that the edema fluid, when carefully collected and analyzed, usually shows a small protein content, in our investigations between 0.1 and 0.5 per cent.

In 1896 Starling [3] performed experiments in edema and lymph formation on dogs. On the basis of his experiments, he discussed the factors involved in edema and lymph formation. The conclusions of Starling painstakingly developed by Schade [4] will for a long time to come form the basis for well founded theories of edema formation in nephritis and in heart failure. According to the Starling-Schade concept there must be a balance between the "effective" hydrostatic pressure in the capillaries and the "effective" osmotic pressure of the plasma proteins. If the "effective" hydrostatic pressure throughout the capillaries is greater than the "effective" colloid osmotic pressure of the blood plasma, there must be a continuous filtration of the blood plasma minus the proteins across the capillary wall into the surrounding tissue spaces. If the lymph flow is unable to remove this filtrate as rapidly as formed, it must accumulate in the tissue spaces and edema must result. The "effective" colloid osmotic pressure is the osmotic pressure of the plasma proteins plus the diffusible ion pressure difference (Donnan effect). It is this "effective" colloid osmotic pressure which we measure in our osmometer.[5] The "effective" hydrostatic pressure is the actual blood pressure within the capillaries minus the pressure of the extracapillary tissue fluid. As a rule, this tissue pressure outside the capillaries, at least in the subcutaneous spaces, and with the body in supine position, is small and probably negligible until edema accumulates when it may be necessary to measure it and subtract it from the actual intracapillary pressure in order to arrive at the "effective" filtering pressure. Whenever tissue fluid or edema fluid begins to accumulate beyond the normal amount the lymph flow increases. When the rate of formation of edema fluid reaches a certain velocity, lymph flow can not keep up with the filtration rate, and more and more edema fluid accumulates and finally becomes clinically demonstrable. When about two quarts of edema fluid accumulate in a leg, it is possible to demonstrate pitting edema.

Figure 1 is a schema which illustrates the elementary process of fluid exchange in the capillaries in what may be called the "basal" state, i.e., when the body is placed in the supine position and the capillaries are all at approximately the right auricular level. According to Landis' [6] measurements, which measurements have been confirmed by us, the average blood pressure at the arterial end of the capillary is 32 mm. Hg and the average blood pressure at the venous end of the capillary is 12 mm. Hg. If it were not for the presence of the plasma proteins there would be a continuous filtration of water and salts from the plasma into the surrounding tissue spaces throughout the entire length of the capillary. The plasma protein particles, serum albumin and globulin, can not pass the ultrafilter membrane of the

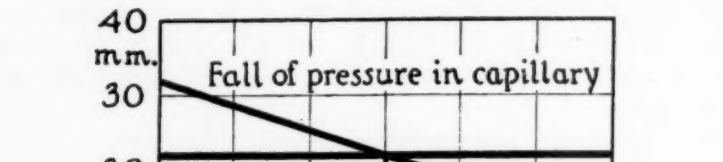

FIG. 1. Graphic representation of fluid exchange in the capillaries of a normal person in supine position. In this position all the capillaries are very nearly at right auricular level.

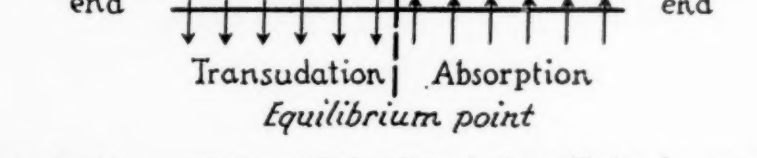

FIG. 2. Graphic representation of fluid exchange in the capillaries of a case of right heart failure in which the capillary pressure at the venous end of the capillary is 20 mm. Hg when the patient is in supine position. With this pressure at the venous end of the capillary, edema will develop when the patient is up and about and on no salt and water restriction.

capillary; they remain behind within the plasma and exert a force tending to resist the filtration of water and salts. The colloid osmotic pressure measures this force exactly. The average colloid osmotic pressure in human plasma is 22 mm. Hg.[7] Where the hydrostatic pressure within the capillary is greater than 22 mm. Hg, water and salts will be filtered out of the blood plasma into the surrounding tissue spaces. Where the colloid osmotic pressure is greater than the hydrostatic pressure within the capillary, water and salt will be transported back from the tissue spaces across the capillary membrane into the plasma. Therefore, in the arterial end of the capillary filtration will take place continuously along the wall of the capillary until a point is reached where the hydrostatic pressure has fallen to the colloid osmotic pressure. From this point onward the capillary pressure decreases continuously and, the colloid osmotic pressure being greater than the hydrostatic pressure, water and salts are brought back into the capillaries. In a state of perfect equilibrium such as is represented in figure 1, which must be looked upon as an ideal case, there is just as much water filtered out of the arterial end of the capillary as is reabsorbed in the venous end. By increasing the capillary pressures at the arterial and venous ends, we can increase filtration above reabsorption. By reducing capillary pressures we can increase reabsorption above filtration. In the one case we get a tendency to edema formation unless the lymphatics can take care of the excess fluid filtered out of the capillaries. In the other case we would get a dehydration of the tissues with a subsequent hydremia of the blood plasma.

Numerous investigators[8] studying dropsy formation in nephrosis and nephritis have proved that edema will tend to form when the colloid osmotic pressure is lowered from its normal value of about 22 mm. Hg to a value of about 15 mm. Hg, unless the intake of salt and water is reduced and the patient put to bed. It would, therefore, seem very probable that if the hydrostatic pressure in the capillaries would rise 7 mm. Hg we would have exactly the same situation in regard to filtration and edema formation as we have in nephrosis and nephritis when the colloid osmotic pressure is reduced 7 mm. Hg. Every clinician who measures venous pressures in right heart failure knows that edema tends to form when the venous pressure reaches about 170 mm. H_2O, a rise of 100–110 mm. H_2O or approximately 7–8 mm. Hg above the normal. Therefore, it seems very probable that our hypothesis is correct, that a rise of intracapillary pressure of 7–8 mm. Hg will be followed by edema formation.

In order to test out this hypothesis it is, of course, necessary to measure accurately the hydrostatic pressure within the capillaries during the formation of edema as well as during the period when edema is absorbing and diuresis is taking place. In order to measure the hydrostatic pressure within the capillary accurately, it is necessary to make direct measurements of this pressure by means of a very small cannula inserted into the capillary. Indirect methods of measuring capillary pressure are wholly unreliable and

give such varying results in the hands of various investigators that they can not possibly be used to solve our problem. Strax and DeGraff [9] have collected the indirect measurements of capillary pressure made by the various investigators. These vary over a range of from 1.5 to 71 mm. Hg. The lower values are such that the tissues would unquestionably soon become completely dehydrated and the higher values would necessarily lead to marked edema formation in normal persons.

In 1926 Landis [10] succeeded in cannulating human capillaries with a very fine micropipette and was able to measure directly by means of a water manometer the actual hydrostatic pressure at the arterial end of the capillary, at the venous end of the capillary, and at the top of the capillary loop, i.e., approximately half way between the arteriolar and the venous end of the human capillary. He made over 100 determinations of intracapillary pressure. The mean pressure at the arteriolar end was 32 mm.; at the height of the loop it was 18 mm., and at the venous end it was 12 mm. Hg.

We have applied Landis' method in our problem of determining the capillary pressure during edema formation and after edema had disappeared in cardiac cases.* The micropipettes are drawn out to a diameter of 8–12 microns from fine glass tubing heated in a flame. They are then clamped in a micromanipulator which allows accurately controlled but very minute movements in the three planes of space. The micropipette is connected by flexible metal tubing to a manometer system. The height of the manometric column is changed by movement of the plunger of a syringe, controlled by a thumb screw. In this way pressure within the pipette is changed. (When equilibrium is established blood corpuscles, which rush into the tip of the pipette when the capillary is pierced, oscillate to and fro with the heart beat. The point of exact pressure equilibrium, which is attained when the corpuscles oscillate about the same point for 5 to 10 seconds without continuous movement either into or out of the pipette, is quite distinct.) The entire system to the tip of the pipette is filled with physiological salt solution to which 0.3 per cent sodium citrate has been added. After the system has been properly filled and is free of air bubbles, the micropipette is driven through the epidermis of a finger a short distance behind the nail. The subjects are placed comfortably in the supine position with the finger at the level of the right auricle. This finger rests snugly in a plasticine mold. The capillary to be pierced, as well as the movements of the micropipette, and the movements of blood from the capillary in and out of the pipette are observed with a Spencer binocular dissecting microscope with a magnification of 85 times. The finger is illuminated with a Spencer universal microscope lamp No. 368.

The normal subjects and the patients are kept comfortably warm and the measurements are made at room temperature on naturally warm fingers. All

* We wish here to acknowledge our obligation to Dr. Landis for his advice in applying his method and for showing one of us (I.E.) how to overcome some of its difficulties.

the necessary precautions for making accurate measurements are taken. The introduction of the micropipette obliquely into the venous end of the capillary does not block flow in most cases and, therefore, the pressure reading on the manometer indicates the side-arm pressure at this point. One does not pierce the extreme venous tip of the capillary, and for this reason we may suspect that the capillary hydrostatic pressure at the extreme venous end of the capillary may be a little lower than the measured pressure. This difference is certainly no greater than 1 mm. Hg. Occasionally some blocking of flow may take place during capillary pressure measurements at the venous end with an occasional measurement higher than the actual pressure within the vessel at this point. The introduction of the micropipette into the summit of the capillary loop usually does not obstruct flow in the capillary and we may, therefore, assume that the measurement is that of the side-arm or hydrostatic pressure at the middle point of the capillary. Blood flow is often partially or completely blocked by the introduction of the micropipette into the arteriolar limb of the capillary loop. As Krogh showed, the length of capillary between the point of entrance of the pipette and the point of origin of the capillary from the arteriole becomes a side-arm of the manometric system and the pressure measured in this portion of the capillary is the lateral (side-arm) pressure in the arteriole at the point opposite the origin of the capillary. There is an error in determining the level of the right auricle which may be as great as 1 mm. Hg in some cases. All in all, it is pretty evident that the error in these measurements of hydrostatic pressure in the capillaries is probably no greater than 1 or 2 mm. Hg. This is just the same order as the error in measuring the colloid osmotic pressure. The biological " scatter," as measured by the standard deviation from the mean of our series of measurements of pressures at the venous end of the capillary on normal subjects, is 2.4 mm. Hg which is the same as the standard deviation for a series of measurements of colloid osmotic pressures on normal plasmas. As the mean value for a series of measurements of colloid osmotic pressure made upon normal persons is 22 mm. Hg and the " mean " hydrostatic pressure measured in the venous end of the capillaries of a series of normal persons is 12 mm. Hg the relative variations or relative dispersions of the values obtained from measurements upon normal subjects is greater in the case of the measurements of capillary hydrostatic pressure made in the venous end of the capillary. Moreover, capillary pressure is undoubtedly variable from capillary to capillary depending upon the state of the arteriole to which each is attached, the state of the veins into which each empties, and the state of dilatation or contraction of each capillary itself, whereas the colloid osmotic pressure is constant in any one individual over a considerable period of time. We believe that capillary hydrostatic pressures made according to Landis' method of direct cannulation of the capillary have the same degree of accuracy as measurements of colloid osmotic pressure of the plasma, and the biological " scatter " or " dispersion " of normal values about

the mean of a series of measurements is only a little greater for capillary pressure measurements than for colloid osmotic pressure measurements made upon a series of normal plasmas.

Table 1 summarizes our measurements of capillary hydrostatic pressure on 16 normal persons.* The average pressure at the venous end was 12 mm. Hg; at the summit of the capillary loop (middle) the "mean" pressure was 20 mm. Hg; and the "mean" capillary pressure at the arterial end was 34. Our average pressure at the arterial end and at the summit of the loop is 2

TABLE I

Normal Capillary Pressure Measurements

Case No.	Capillary Pressure *		
	V	T	A
1	18		
2	15		
3	12		
4	12	18	30
5	12		
6	12	20	40
7	15		35
8	10		30
9	10		35
10	10		
11	10		
12	15		
13	12		35
14	11		
15	10	20	
16	11	24	35
Range	10–18	20–24	30–40
Average	12.2	20.4	34.3
P.E.(c)	1.6		

* = mm. Hg
V = venous limb
A = arteriolar limb
T = summit of capillary loop
P.E.(c) = probable error (corrected for small sample analysis).

mm. Hg higher than Landis' average for these points along the capillary pressure gradient. The probable error of the pressure measurements at the venous end of the capillary corrected for small sample analysis is 1.6 mm. Hg or a standard deviation of 2.4 mm. Hg. These measurements confirm Landis' more extensive normal capillary pressure measurements. They indicate that the method gives consistent results in the hands of other investigators when they have learned the technic.

Table 2 summarizes our capillary pressure measurements in nine cases of right heart failure with edema present. The heart failure in these cases was due to rheumatic or arteriosclerotic heart disease. Moderate to severe edema

* The capillary pressure measurements in this study were made by one of us (I. E.) as part of a thesis in partial fulfillment of the requirements for the degree of Master of Science in Medicine in the Graduate School of the University of Minnesota.

was present at the time of the study in all cases and diuresis had not yet set in, except in case 9. This case, whose capillary pressure in the venous limb was 20 mm. Hg, started to have a moderate diuresis during the 24 hour period in which the capillary pressure measurement was made. His urine output on this day was 1800 c.c. as compared with fluid intake of 800 c.c. The patient was at rest in bed during this day, and it is also possible that the capillary pressure dropped somewhat after the pressure measurement was made and within the 24 hour period during which the fluid output was measured. This capillary pressure is undoubtedly the critical point in capil-

TABLE II

Capillary Pressure Measurements in Cases of Right Heart Failure with Edema

Case No.	Capillary Pressure *		
	V	T	A
17	25		
18	30		
19	35		
20	25		
21	35		
22	25		
23	40		
24	24		
25	20		
26†	18		
27†	18	25	

* = mm. Hg
V = venous limb
T = summit of capillary loop
A = arteriolar limb

† *Case 26* Subacute or chronic glomerulonephritis with edema. Serum albumin 2.2, serum globulin 1.4, total plasma protein 3.6. Colloid osmotic pressure 7 mm. Hg.

† *Case 27* Chronic glomerulonephritis with edema. Serum albumin 2.8, serum globulin 2.7, total plasma protein 5.5. Colloid osmotic pressure 13.5 mm. Hg.

lary pressure. With the patient lying in the supine position in bed, edema may or may not develop at this point. Certainly if the patient is up and about with the capillary pressure in the lower extremities increased by the weight of the column of blood between the right auricular level and the limb level, edema will tend to accumulate when the capillary pressure is as high as 20 mm. Hg at the venous end. In the other eight cases in this series of measurements the output of fluid was not above the intake. It must be borne in mind that with the accumulation of edema to the visible point there is an increase in the pressure of the extra-capillary fluid which tends to cause absorption of edema if the patient is put in the supine position, unless the capillary pressure in the venous end is at the colloid osmotic pressure level or above. We have three subjects in whom the capillary pressure in the venous limb was 18 mm. Hg. One was a normal subject without edema and the other two were cases of glomerulonephritis. These latter two cases had edema, but the colloid osmotic pressure in one of these cases was lowered

to 7 mm. Hg and the other to 13.5 mm. Hg. In these latter two cases the drop in colloid osmotic pressure alone would favor increased filtration and edema formation.

Our figures are in good agreement with the findings of Krogh, Landis and Turner [10] and Landis and Gibbons.[11] Using plethysmographic methods these authors were able to detect filtration when the venous pressure was elevated 9 mm. Hg above normal. Our measurements, although few in number, would seem to indicate definitely that edema formation takes place in right heart failure when the capillary pressure in the venous limb is increased 8 mm. Hg, provided the patient is up and about and is not on a salt free diet. If this patient is then put to bed and fluid and salt intake are restricted, diuresis will tend to develop. When the capillary pressure in the venous end is more than 8 mm. above the normal, edema will not tend to disappear until the pressure in the capillaries drops to a point close to 8 mm. above the normal capillary pressure.

TABLE III

Capillary Pressure Measurements in Cases of Right Heart Failure with Edema and Following Relief of Edema

Case No.	Capillary Pressure *			Remarks
	V	T	A	
28	25			Marked edema
	12	18	30	Edema gone
29	30			Marked edema
	15			Edema gone
30	20			Moderate edema
	11	24	35	Edema gone

* = mm. Hg
V = venous limb
T = summit of capillary loop
A = arteriolar limb

In the second column of table 3 we show capillary pressure measurements made on three other cases with right heart failure during the period when the patients had edema and diuresis had not yet started, though the patients were in bed with restricted intake of salt and water, and in the third column we show the capillary pressure after diuresis had started and edema was no longer present. It will be noted that in all cases the capillary pressure in the venous end during edema formation is 20 mm. or more. After diuresis is started and edema has disappeared, capillary pressures in the venous end of the loop are 15 mm. Hg or less. This table shows that during the period of edema formation capillary pressure is elevated 8 mm. Hg or more and that after the diuresis starts and edema begins to disappear, capillary pressures have returned to the normal.

We also investigated the capillary pressure in eight cases of marked left heart failure with marked dyspnea, passive congestion of the lungs and cyanosis, but in whom no edema was present and in whom the fluid output

equalled the fluid intake. The results of these measurements are shown in table 4. In all eight cases where severe left heart failure was present but no edema was present, we noted that our measurements indicate that the capillary pressures are well within the normal range. This again shows that even in heart failure with lowered oxygen content of the venous blood, as long as the capillary pressure does not rise 8 mm. or more above the normal, no edema will form.

TABLE IV

Capillary Pressure Measurements in Cases of Left Heart Failure (no edema)

Case No.	Capillary Pressure * V	T	A
31	12		
32	10		35
33	10		
34	12		
35	12	18	30
36	15		
37	11		
38	11	24	35
Average	12	21	33

* = mm. Hg
V = venous limb
T = summit of capillary loop
A = arteriolar limb

In table 5 we show the capillary pressure measurements in four cases in which there was no heart failure present at the time of these measurements but in which the capillaries were at least twice the normal diameter. In other words, no edema was formed when the capillaries were widely dilated as long as the capillary pressures were well within the normal range. Therefore, up to a certain point dilatation of the capillaries is not a very significant factor in edema formation. The reason for this is easy for anyone to see. Unless the capillaries become more permeable to protein, thus causing a colloid osmotic pressure on the outside of the capillary and tending to aid the

TABLE V

Capillary Pressure Measurements in Millimeters Hg in Various Clinical Conditions Associated with Dilated Capillaries without Edema

Case No.	Capillary Pressure * V	T	A	Diagnosis
39	12	20	40	Congenital heart disease
40	15		35	Polycythemia vera
41	10		30	Polycythemia vera
42	10			Scleroderma

* = mm. Hg
V = venous limb
T = summit of capillary loop
A = arteriolar limb
All cases in the above group had capillaries at least two times normal size.

passage of water across the capillary loop and to decrease the absorbability at the lower end of the capillary loop, there is just as much increased rate of reabsorption in the capillary in its lower end as there is increased filtration at its upper end in the supine position. These experiments, in our opinion, prove that the hypothesis that edema formation in right heart failure is due to elevated capillary hydrostatic pressure is well founded, and there is no necessity for bringing in any other mechanism than increased capillary hydrostatic pressure to explain the edema formation. The Starling-Schade mechanism of edema formation now comes in the realm of theory and is no longer one of pure hypothesis either in nephritis or in heart failure.

The capillary pressure at the venous end of the tube is 7–8 mm. Hg above the venous pressure measured in the basilic vein of the arm. Therefore, when the capillary venous pressure is 20 mm. Hg the venous pressure in the arm vein is 12–13 mm. Hg or 15.7–17.6 cm. of H_2O. Many clinicians have observed that edema of the lower extremities will appear when the venous pressure is 17 cm. of H_2O or above unless the patient is put on restricted salt and water intake or put to bed in the supine position. After this work had been finished, and it seemed definitely proved that edema must appear when capillary and venous pressures rise 8 cm. of mercury above the normal value, two cases of heart failure, the one a mitral stenosis with tricuspid insufficiency and auricular fibrillation, the other a supposed congenital heart with associated tricuspid insufficiency and auricular flutter, both with large pulsating livers, came into the hospital. These patients had severe dyspnea, markedly enlarged hearts, large pulsating livers, and a high degree of cyanosis but did not exhibit peripheral edema. The venous pressure of the one with mitral stenosis was 20 mm. Hg. The pressure at the venous end of the capillary of the finger would, therefore, be at least 27 mm. Hg. This observation would seem to overthrow the Starling-Schade concept of balance between colloid osmotic pressure and hydrostatic pressures within the capillaries. If the colloid osmotic pressure in this blood were 22 mm. Hg, the capillary pressures throughout the whole capillary would be much higher than this and there would be an excessive continuous filtration of plasma minus the proteins out into the pericapillary regions with the formation of edema. This apparent exception to the rule was soon proved to be an experiment that actually supports the rule because the plasma proteins were determined as 8.9 gm. per cent of which 6.0 per cent was albumin and 2.9 per cent globulin. The osmotic pressure as determined in our osmometer was 36.0 mm. Hg and, therefore, the capillary pressure at the venous end is 9 mm. Hg below the colloid osmotic pressure which is the normal relationship. In the second case the venous pressure in the arm vein was 16 mm. Hg corresponding to a hydrostatic pressure of 23 mm. Hg at the venous end of the capillaries. If the colloid osmotic pressure were the normal one of 22 mm. Hg edema would have to form. But no edema was present. This patient also had an increased plasma protein content of 8.4 per cent, of which albumin was 5.7 per cent, globulin 2.7 per cent, and the colloid osmotic pressure as determined

in our osmometer was 33.0 mm. Hg. In this case the colloid osmotic pressure was 10 mm. Hg above the hydrostatic pressure at the venous end of the capillaries, which is again the normal relationship. These two exceptions to the rule, when carefully investigated, become excellent proofs that the rule apparently holds that when the colloid osmotic pressure is no more than 2–3 mm. Hg above the hydrostatic pressure in the venous end of the capillary, edema tends to form. In both of these cases the degree of anoxemia in the tissues must have been as great as is usual in heart failure with edema formation. The first case has had a high degree of cyanosis for years during which time her auricles have been fibrillating. We know from Kerkhof's [9] measurements that cases of mitral stenosis with auricular fibrillation have minute volumes at least no greater than 70 per cent of the normal and probably much less even after the heart has been well digitalized. The case of supposed congenital heart with associated tricuspid insufficiency had auricular flutter for many months before these measurements were made and we can infer both from this and the degree of cyanosis that there must have been at least as much anoxemia present as in the average case of heart failure with edema and cyanosis. Yet in neither of these cases was edema present despite the fact that they were both up and about. These two cases, as well as the eight cases of table 4, seem definitely to refute the idea that the degree of anoxemia present in heart failure is sufficient per se to cause edema formation. In the presence of cyanosis, edema does not occur provided the colloid osmotic pressure is 3 or more mm. Hg above the capillary pressure at the venous end or 11 mm. Hg above the venous pressure in the arm.

Peters [10] and other investigators have shown that the plasma proteins are sometimes reduced in heart disease and in consequence the colloid osmotic pressure must be lowered. As a rule this lowering of colloid osmotic pressure is not great, but it may in rare cases become a prominent factor in edema formation. Therefore, in all rigorous investigations of edema tendency it will be necessary to measure both the colloid osmotic pressure of the plasma as well as the hydrostatic pressure in the capillaries. Colloid osmotic pressure determinations with the Schade osmometer [11] are more easily and more quickly carried out than plasma protein determinations. For clinical investigations they can be carried out in a room in which there are no sudden variations in temperature and no air currents. The osmometer acts only as a thermometer for very short periods of time. If the measurements are made at a room temperature of 20° C., it is necessary to correct the value obtained by multiplying by 1.06 in order to get the osmotic pressure at the body temperature of 37° C. The hydrostatic pressure in the capillaries is difficult to measure and time-consuming. But it is not necessary to measure the hydrostatic pressure in the capillaries. The pressure at the venous end of the capillary is approximately 7 mm. Hg higher than the venous pressure as measured in the arm vein. For all but the most rigorous investigations the calculation of the capillary pressure at its venous end from the venous pressure measured in the arm is sufficiently accurate. In fact, we can state the

rule for edema tendency, where capillary permeability is not qualitatively changed and where lymph obstruction is not present, as follows: Edema tendency is present when the venous pressure measured in the arm vein is not more than nine millimeters below the colloid osmotic pressure of the plasma. Remembering that the probable error of osmotic pressure determinations is 0.4 mm. Hg and that the error in making venous pressure determinations is of the order of 1 mm. Hg, we should not expect our measurements to fit the above rule by better than 1–2 mm. Hg. Considerable experience in applying the above rule in this clinic has shown that the observations fit the rule in the majority of cases within 1–2 mm. Hg.

Conclusions

1. The cause of edema formation in right heart failure is the rise in capillary hydrostatic pressure. Anoxemia probably plays no essential part in edema formation in right heart failure.

2. A tendency to edema formation develops when the hydrostatic pressure in the venous end of the capillaries rises to within 2 mm. or less of the colloid osmotic pressure. If the patient is up and about, if no precautions are taken as to salt and water restriction, and if no diuretics are given, edema will develop.

3. If the colloid osmotic pressure is the normal of 22 mm. Hg, edema tendency is present if the hydrostatic pressure in the venous end of the capillary is 20 mm. Hg or the venous pressure in the arm vein is 13 mm. Hg or 17 cm. H_2O.

4. A drop in colloid osmotic pressure of 7 mm. Hg or a rise in capillary pressure of 8 mm. Hg produces approximately the same edema tendency.

5. Edema tendency is present when the colloid osmotic pressure is not more than 9 mm. Hg higher than the venous pressure in the arm.

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INFLUENZA *

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Investigations of influenza have been beset with serious difficulties since first they were begun. Acute upper respiratory diseases tend to resemble each other very closely and, as is well known, their classification on clinical grounds has not been very successful. One of the chief difficulties is the lack of definite objective signs, except for fever and minor alterations in the appearance of the mucosa of the upper respiratory tract. Unfortunately, there is no sharp line between the symptomatology of a severe common cold, sporadic grippe, and influenza. The manifestations of these symptom-complexes shade imperceptibly one into another, and the difficulties of classifying individual cases as examples of any one of these varieties of acute respiratory diseases are often insurmountable. Various attempts [1, 2, 3, 4, 5] have been made to establish clinical criteria upon which a diagnosis of influenza might be based, but even among cases in which the etiology of the disease was determined no pathognomonic signs or symptoms were discovered. Almost the only characteristic which serves partially to distinguish influenza from other acute respiratory diseases is a tendency toward epidemicity. However, since epidemics of influenza usually tend to occur at periods when there are also marked increases in the incidence of the other conditions mentioned, even this characteristic loses much of its significance.

An even greater handicap which confronts the student of influenza is the lack of a suitable experimental animal. At the present time ferrets and hamsters are the only known species sufficiently susceptible to infection by the human viruses to be useful. But neither of these species develops a disease which simulates closely that observed in human beings. The hamster fails to show any visible manifestations of infection, and the fact that infection by either of the two known influenza viruses has occurred can be demonstrated only by serological test.[6] The ferret may develop fever and show certain suggestive symptoms, but these have been found to be very unreliable indicators of the presence of infection by human influenza viruses,[4] and consequently with this species it is also necessary to carry out neutralization tests if accurate information is to be obtained. Although ferrets have been very valuable in studies on the etiology of influenza and their use was directly responsible for the initial discovery of influenza viruses, work with them is difficult, laborious, and expensive. These animals are so susceptible to distemper that a special isolation technic is essential if months of work are not to be rendered futile by an outbreak of this extremely infectious disease. For reasons which are not understood, it has become increasingly difficult

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to recover virus by the use of ferrets from the throats of patients who were shown by serological tests to have influenza A.[4, 5] This suggests either that ferrets are not particularly susceptible to the human virus or that too small quantities of the virus were present in the specimens studied. Whatever the explanation, it is obvious that epidemiological studies based on the recovery of virus from cases of influenza can have at the present time but limited value.

Mice are not susceptible to human influenza viruses. Viruses which become established in this species must first go through a long series of passages before any evidence of infection is produced. Whether or not significant modifications in the virus are induced by this process is unknown. It seems entirely possible, however, that this long process of adaptation may alter other characteristics besides species pathogenicity. It may be of importance to keep this possibility in mind in attempting to interpret results obtained with so-called mouse-adapted strains.

Despite these serious limitations to investigation of influenza, a considerable body of data relating to this illness has been amassed, and it is now known that the epidemic disease may be due to any one of at least three infectious agents. Two of the causes of influenza have been discovered and are known to be viruses. The first, now spoken of as influenza A virus, was described by Smith, Andrewes, and Laidlaw [7] in 1933. The second, termed influenza B virus, was described independently and almost simultaneously by Magill [8] and Francis [9] in 1940. Although no other causal agent has as yet been discovered, the evidence that at least a third agent exists is equally as good as that upon which are based the causal relationships of the two known viruses. During the past year, of more than 850 cases of influenza studied in our laboratory, approximately 30 per cent showed no evidence of infection by either influenza A or influenza B virus and remain, therefore, of unknown cause.

Unfortunately, epidemics of influenza do not seem to be homogeneous as regards the cause of individual cases. In a recent study of outbreaks of the disease in 15 institutions, we found no instance in which evidence could be obtained that all cases studied were due to the same infectious agent. In some institutional epidemics studies of throat washings and sera indicated that at least three etiological varieties of influenza were present simultaneously, while in most institutional outbreaks similar data suggested that at least two distinct kinds of the disease occurred concurrently. Consequently, it seems reasonable at the present time to think that any case in a given epidemic may be caused by one of at least three different infectious agents.

One of the most important problems in influenza is immunity to the disease. Since the therapy of almost all virus diseases is disappointing at best, and since so far no therapeutic agents which significantly modify the course of influenza have been discovered, it is probable that the most hopeful procedure for the control of this disease lies in induced immunity to it. The

fact that the clinical syndrome called influenza includes a number of distinct etiological entities makes it impossible to discuss immunity to these diseases collectively, since it is not yet known that what is thought to apply to influenza A will also be applicable to influenza B or to the influenzas of unknown cause.

For quite obvious reasons it is not feasible to determine whether a given individual is immune or susceptible to influenza A directly. However, it is possible to measure with considerable accuracy the quantity of circulating antibodies against mouse-adapted influenza A virus possessed by different individuals. This has been done under carefully standardized conditions in over 1300 apparently normal persons residing in areas in which epidemics of influenza had not occurred for at least two years. It was found that there were very wide differences in the amount of antibody present in the sera of certain individuals (10). The great majority, over 95 per cent, of adults possessed measurable quantities of antibodies against the virus, but whereas approximately 20 per cent had very small quantities, another 20 per cent had large amounts, and the remaining 60 per cent were distributed in the various antibody ranges between these two extremes.

The marked differences between the quantities of antibodies against influenza A virus possessed by various normal individuals remained of merely academic interest until it was found that they actually were one expression of relative immunity to the disease itself.[10] In more than 200 individuals who contracted proved influenza A a study was made of the serum antibody levels either prior to the onset of the disease or in the first days of the illness before it was likely that additional antibodies would be produced.

A comparison between these results and those obtained in normal individuals has shown that considerably more cases of influenza A occurred in persons with the lowest antibody levels than were to be expected on the basis of the distribution of antibody levels among normal human beings. This suggested that persons with low levels of antibodies against the virus were relatively susceptible to influenza A. Conversely, fewer cases of the disease occurred in persons with high antibody levels than would have been anticipated on the same basis. This suggested that individuals with high antibody levels were relatively immune to influenza A. It is of importance to point out that no critical antibody level was found which assured complete immunity against the disease in any individual case and that a few individuals in the highest antibody range were found to have contracted influenza A.

The evidence that there was a definite correlation between high antibody levels against influenza A virus and relative immunity to the disease itself was of considerable importance since it afforded a rational basis upon which to attempt prophylactic immunization against influenza A. It seemed probable that if it were possible to increase antibodies against the virus to sufficiently high levels in a given population, the incidence of influenza in an epidemic might thereby be reduced.

An attack of influenza A tends to increase antibodies against the virus

markedly during convalescence. This fact is utilized in establishing an etiological diagnosis by laboratory tests.[11] Unfortunately, the high antibody levels achieved during convalescence do not persist indefinitely, but rather rapidly decrease with time. On the basis of antibody studies carried out at successive intervals after the disease, it seems probable that one attack of influenza A did not result in an enduring immunity and that at least 60 per cent of the cases studied could have been reinfected by the same virus within one year of their illness.[12] This deduction has not yet been verified directly since so far there has been no opportunity to study two attacks of influenza A in the same individual. If, as seems likely, the disease itself does not confer lasting immunity, it is highly improbable that any artificially induced immunity would possess any more durable quality.

It has been shown [13, 14] that the parenteral injection of active or inactivated influenza A virus stimulated the production of increased quantities of specific antibodies although no clinical illness was produced. This fact has been utilized as a basis for attempts at prophylaxis against the disease. Various kinds of vaccines have been used, and groups of vaccinated and control individuals have been followed through epidemics of influenza. The results have been contradictory in that while some investigators [15, 16] found reductions in the incidence of clinical influenza among vaccinated persons, others [2, 17] observed no significant diminution in the frequency of the disease following vaccination.

Recently a vaccine, somewhat different from those previously tried against influenza A, was developed.[18] This vaccine was prepared from chick embryos inoculated with both influenza A virus and the X strain of canine distemper virus. Earlier experiments had demonstrated that a complex vaccine of this kind was very effective in immunizing ferrets against experimental influenza A.[19] After it was found that the complex vaccine stimulated the production of considerably more antibodies against influenza A virus than any of the other vaccines tested in human beings,[18] an effort was made to determine whether this vaccine would actually produce any significant degree of immunity against the disease itself.

Large groups of persons in various institutions in different parts of this country were given a single subcutaneous injection of the complex vaccine during last fall. Somewhat larger groups in the same institutions were left as unvaccinated controls. Four months after the vaccine had been given, outbreaks of influenza occurred in a number of these institutions. Because it had been found that the etiology of influenza was diverse and since the vaccine was directed only against influenza A, it was considered essential to determine by laboratory tests the etiology of as many cases as possible in both the control and the vaccinated groups. Without the information gained by this extensive study it seemed impossible to make any accurate assessment of the possible efficacy of the vaccine as a prophylactic agent against influenza A.

Almost all of the laboratory studies on throat washings and sera obtained from cases in these outbreaks have been completed. It was found that there were wide differences in the proportion of cases of influenza in the control groups which showed evidence of having been infected by influenza A virus in various institutions. For example, in one institution only 53 per cent of the clinical cases were of this variety, while in another 92 per cent of the cases were caused by this virus. Although lots of vaccine of approximately equal antigenic potency were used in each of these institutions, there was considerable variation in the results observed in various institutions. In one institution there was no difference between the incidence of influenza A in the control and vaccinated groups. In all the other institutions studied, however, the incidence of this disease was somewhat lower among vaccinated persons than among control individuals. These reductions ranged from a 30 per cent to a 90 per cent decrease in the occurrence of influenza A when compared with the incidence of the same disease among the controls. Considered collectively, it was found that influenza A had occurred in about 6 per cent of the control individuals and in about 3 per cent of the vaccinated individuals of these institutions. This indicates that a decrease of approximately 50 per cent in the incidence of the disease was observed among the vaccinated groups.

Obviously these results do not indicate that a satisfactory and trustworthy immunizing agent against influenza A has been found. On the other hand, the reduction in incidence observed is not negligible and suggests that at least a step, however small, has been made in the direction of the eventual control of this disease. Furthermore, the results obtained tend to confirm the available evidence concerning the relationship between high antibody levels and relative immunity to influenza A and therefore may serve to point the way toward more effective prophylaxis. It seems possible that should a vaccine of considerably greater potency become available and should this improved vaccine increase specific antibodies to even higher levels, somewhat more striking reductions in the incidence of influenza A might be expected to result from its administration. Although these are intriguing problems for the future, it should be emphasized again that influenza A is merely one etiological variety of influenza. Until such a time as those other unknown causes of the disease are discovered, it will hardly be possible to develop satisfactory prophylactic measures against epidemics of influenza as such.

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THE PRINCIPLES UNDERLYING THE TREATMENT OF CARDIOVASCULAR SYPHILIS *

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FROM the first therapeutic efforts to effect cure to the present moment, the treatment of syphilis has been in a state of perpetual flux. The turnover in the treatment formulae is so rapid that almost every decade sees new methods, newer drugs, superseding those hailed as the last word and the accepted dicta of the preceding like period.

Biological, pathological and bacteriological studies of the past quarter century have led to a much broader concept of the pathology of syphilis and have projected into its clinical aspects many systemic syndromes previously believed to be of other etiology. These numerous entities affecting the osseous, the gastrointestinal, but more particularly, however, the neurological and cardio-vascular systems, have diversified and influenced the various accepted treatment formulae.

For early syphilis in its septic period, and for the many-sided cutaneous and mucous membrane lesions and relapses we may with few qualifications accept standard treatment formulae. When, however, we approach the field of late syphilitic sequelae, particularly those affecting such vital structures as the viscera and the nervous system, standardized treatment must be modified or even replaced by therapeutic efforts directed to the particular system involved and the degree of involvement present.

The therapeutic approach to system syphilis is further modified by the immediate type of the pathologic changes present. Late syphilitic disease wherever found is characterized by two distinct types of lesions, either one of which, or both, may be present. First are such lesions as isolated gummas and diffuse syphilomatous processes accessible and amenable to therapeutic agents. Lesions of this type may exist in various structures, frequently silent, and even when extensive they may exist without causing any appreciable dysfunction of the affected organ. Of greater importance are the mechanical defects resulting from such lesions, and the replacement of normal and diseased tissues by fibrosis, calcification and other degenerative changes. Lesions of this type are not only uninfluenced favorably by treatment, but because of the weakened structures involved and the toxicity of the drugs used, treatment may make them distinctly worse.

In no structure of the body is this better exemplified than in the cardiovascular system. Where late syphilis has affected the heart and great blood vessels, one is faced not only with the necessity for a careful evaluation of the type of lesion present and the choice of a kind and the amount of drug in-

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dicated, but very frequently one may have to decide that no treatment of a specific nature is indicated.

An experience of over 30 years with a large number of the variegated types of cardio-vascular syphilitic disease, and stimulated more by earlier mistakes than by successful procedures, I have come to the firm belief that one cannot postulate definitely as to the management of this large group as a whole but, guided by certain underlying principles, each case from its therapeutic and prognostic outlook, must be regarded as an individual problem. A definite plan, therefore, of treatment for the syphilitic heart and aorta cannot be axiomatically laid down.

The need for individualization and careful appraisal of each case is at once evident if we review briefly the factors which must be considered. Of almost equal weight in this respect are such data as the age of the patient, the duration of the infection, the background of previous treatment or its absence, the type of the lesion present, the existence or preëxistence of decompensation or failure.

While we are considering, for the most part, the treatment of the late cardiovascular sequelae, attention should be drawn to the fact that in rare instances involvement of a more or less serious nature may occur precociously as a manifestation of the earlier period. Cases of this kind represent a small, little recognized, and relatively unimportant group. In a very small number of personal observations I have seen arrhythmia, tachycardia, heart block and sudden attacks of syncope in the exanthematous period of the disease which would seem to have indicated early involvement of the myocardium. Sudden death from heart failure has been recorded in a small number of such cases. It would seem not unlikely that involvement of this type may be the result of spirochetal invasion in structures previously damaged from other causes. From the few cases of this type observed, no especial treatment appears to be indicated and the therapeutic response to general systemic measures as laid down for early syphilis, plus bed rest, has been satisfactory.

The large group of cases of syphilitic cardiovascular disease may be separated into four distinct groups for special consideration. *First:* cases with signs and no symptoms which have had previous energetic treatment directed to their constitutional infection. *Second:* cases in which treatment has been energetic early, but in which definite cardio-vascular dysfunction exists. *Third:* cases with signs and no symptoms in which inadequate or no previous treatment has been given. *Lastly:* cases with both signs and symptoms in which the treatment has been absent or inadequate. To these four groups, a fifth may be added in which symptomatic and asymptomatic cardiovascular disease exists with other predominant visceropathies.

In the first group, many of whom represent people in late life with fully compensated lesions, the physician is frequently justified, even in the presence of serological evidence and physical signs, to withhold all treatment. The

majority of such cases are those of well compensated aortic regurgitation and also included in them are a few cases of subclinical aortitis and diffuse aortic dilatation. I have seen many such cases in people of advanced years endlessly and vainly treated in a futile effort to reverse a positive blood test. In this type the continuous barrage of heavy metals and particularly of arsphenamines, may do more harm than good. Such overtreatment indicates a failure properly to evaluate and appraise the individual factors present.

In the second group, those who have been energetically treated before the onset of clinical cardio-vascular disease, I would go even further and state rather categorically that during the stage of decompensation or failure, such cases should seldom, if ever, receive treatment directed to their syphilitic infection. The immediate problem in these cases is not the treatment of active syphilomata, but is one of heart failure, the result of degenerative changes which cannot be appreciably influenced by treatment directed to the old syphilis.

The most favorable cases from the standpoint of therapeutic response following judicious anti-syphilitic treatment, are those included in group three in which cardiovascular disease exists with signs and no symptoms and in whose background there has been inadequate, or no treatment. To what extent the degenerative changes in these cases are inhibited or slowed down by treatment, to keep the lesions asymptomatic, is difficult to determine. No one, however, who has seen such cases in large numbers can fail to be impressed by the fact that many remain stationary, their physical signs remaining constant or even occasionally changing for the better. Dysfunction and failure in such cases seem definitely postponed. The benefit derived by such patients from a non-intensive, but continuous, form of treatment must be due in part to the absorption of syphilitic residua in other parts of the body than in the circulatory system, as well as from the effects of the treatment upon syphilitic residua in the appreciably affected organs. The presence and persistence of syphilitic foci remote from the heart must be recognized as a contributory factor in the ultimate failure in untreated cases.

In the fourth group, which includes those cases which have been inadequately treated early and in which definite cardiac dysfunction exists, the physician is faced with a very delicate therapeutic problem. As in the second group, such cases should seldom, if ever, be treated for syphilis during the stage of their decompensation. When, however, compensation has been restored, following rest and measures directed toward the immediate mechanical defect, judicious treatment on conservative lines is occasionally of unusual benefit. Here again such beneficial effect must be ascribed in part to the response of the remote syphilitic lesions in other parts of the body. With regard to the specific remedies to be employed, I believe the arsphenamines, generally speaking, have little or no place in the treatment of cardio-vascular disease. Occasional cases may be markedly benefited when small doses of these drugs are combined with the heavy metals and the iodides. I am

quite convinced, however, that a plan of treatment, based upon the heavy metals together with rest and iodides, has resulted in an equally large number of successfully treated cases with fewer unhappy results than occur with the arsphenamines. A series of unfortunate experiences in which I had seen the intensive use of the arsphenamine actually produce dysfunction and not infrequently death, leads me to advise against them in cardio-vascular syphilis.

However, with the introduction of tryparsamide and its suggested use in neuro-syphilitic disease, I was early convinced of its singular beneficial effect in certain cases of cardio-vascular syphilis, especially in occasional early aortitis and early aortic dilatation. Although this drug has failed to produce all of the expected happy results in neuro-syphilitic disease for which it was intended, it seems to have an extraordinary tonic effect and its judicious use is occasionally attended with a remarkable improvement in color, strength and weight, so that it merits consideration together with the heavy metals where treatment is indicated.

Summary

1. The fundamental principles governing the treatment of cardio-vascular syphilis embrace the careful appraisal of each case with regard to the therapeutic response which might reasonably be expected from the type of lesion present.

2. Cases in which failure is present should receive treatment no different from that given heart failure from other causes.

3. Cases most favorably influenced by anti-syphilitic treatment are those in which physical signs exist without symptoms, and in which there has been little or no previous anti-syphilitic therapy.

4. Asymptomatic cases in which treatment directed toward syphilis has been energetic in earlier years, may often be singled out as patients who need no treatment whatever.

5. The beneficial effects of anti-syphilitic treatment upon cardio-vascular syphilis are in a measure the result of the treatment with the drugs of choice upon subclinical syphilitic lesions in parts of the body remote from the heart itself.

6. Intensive treatment, such as is given in early syphilis, is seldom indicated in the late cardio-vascular sequelae. Although beneficial results may be noticed with conservative arsphenamine therapy, the heavy metals, generally speaking, are considered safer and productive of equally satisfactory therapeutic response.

HYPERTENSIVE HEART DISEASE OF 10 TO 20 YEARS' DURATION; REPORT OF 11 CASES *

By NATHAN FLAXMAN, M.D., *Chicago, Illinois*

IT has gradually become recognized that many persons with heart disease may live long and active lives.[1] This seems to apply especially to cases of coronary artery and hypertensive heart disease. Isolated long-lived cases of the former etiology have been reported from time to time, but only one article, that of Janeway,[2] mentions many long-lived hypertensive patients. In this classic treatise on hypertensive heart disease, Janeway [3] included 51 patients living more than 10 years from the onset of the first important symptoms. Both Riesman [4] and Fahr [5] stressed the fact that the life expectancy in hypertension is much longer than most physicians are accustomed to believe.

In a previous study on the course of hypertensive heart disease [6] it was noted that a significant number of patients, although very small in comparison with the remainder, had lived or were living five to 20 years after the appearance of the first symptom, and a lesser group had lived or are living five to eight years after the occurrence of congestive heart failure. In another study [7] the story of a known hypertensive of 22 years' duration was cited; this man had become decompensated four years previously and at this writing has had hypertensive heart disease over 26 years.

TABLE I

Duration of Hypertensive Heart Disease

Years	No.	%
10	2	18.2
11	1	9.1
12	4	36.3
15	1	9.1
16	1	9.1
19	1	9.1
20	1	9.1
Average—13.7 years		

Recent optimistic reports on the results obtained with so-called specific surgical treatment for essential hypertension have failed to take into account the fact that some hypertensive patients live many years without such operations. To emphasize this fact, the present report includes the case histories of 11 patients with hypertensive heart disease who lived 10 to 20 years (average 13.7 years) after the onset of cardiac symptoms (table 1). In most instances the exact duration of the high blood pressure was not known;

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however, it may be assumed that in all cases the hypertension was present before failure of the hypertrophied heart occurred. There were five males and six females whose ages varied from 25 to 70 years (table 2). Five had regular sinus rhythm, four had auricular fibrillation, the tenth had a bundle

TABLE II
Age Groups at the Onset

Ages	No.	%
25–31	1	9.1
31–40	3	27.3
41–50	2	18.2
51–60	3	27.3
61–70	2	18.2
Totals	11	100.0

branch block, and the eleventh had multiple ventricular extrasystoles. Apparently neither the cardiac rhythm nor the age group had any particular influence on the longevity of these hypertensive patients.

TABLE III
Age Groups at Death

Ages	No.	%
41–50	2	18.1
51–60	3	27.3
61–70	3	27.3
71–76	3	27.3
Totals	11	100.0

CASE REPORTS

Case 1. S. K., a housewife, first learned that she had high blood pressure at the age of 56. When she was 62 she began to have increasing dyspnea. During the pre-cardiac stage her blood pressure varied from 220 mm. Hg systolic and 160 mm. diastolic to 160 mm. systolic and 110 mm. diastolic. The transverse cardiac diameter gradually increased from 12 to 17 cm. She took digitalis, as prescribed for the left ventricular failure, did light housework only, and got along very nicely for many years. Eight years later, at the age of 70, congestive heart failure and auricular fibrillation appeared. The blood pressure dropped to 140 mm. Hg systolic and 90 mm. diastolic. She died at the age of 72 with generalized anasarca. An autopsy revealed eccentric hypertrophy of the heart, which weighed 570 grams, cardiac cirrhosis, marked passive congestion and a sugar-coated spleen, hydrothorax, ascites, and passive congestion of the kidney, stomach, and intestines.

A known hypertensive of 16 years' duration, this woman lived 10 years after the onset of cardiac failure.

Case 2. J. K., a white male retired by the depression of the last decade, complained of marked dyspnea at the age of 64. Physical examination revealed a blood pressure of 220 mm. Hg systolic and 120 mm. diastolic, and a transverse measurement

of 15 cm. Crepitant râles were present at the bases of both lungs. He responded well to digitalis, limited his activity, and went along fairly well for the next 10 years. Whenever he discontinued the digitalis, dyspnea returned and became a prominent symptom. At the age of 74 he developed a rapid auricular fibrillation which precipitated severe congestive heart failure. He died two days after the onset of the arrhythmia. An autopsy revealed eccentric hypertrophy of the heart, which weighed 625 grams, arterio- and arteriolosclerosis of the kidneys with multiple cyst formation, edema and emphysema of the lungs, chronic passive congestion of the liver, spleen, and intestines, hydrothorax and ascites, and edema of the lower extremities.

Although his high blood pressure was not discovered until he entered the cardiac stage, the hypertension was of much longer duration. He was fortunate enough to live 10 years after the onset of left ventricular failure simply by taking digitalis and limiting his activity.

Case 3. M. S., a housewife, complained of dyspnea at the age of 52 years. On physical examination a blood pressure of 190 mm. Hg systolic and 130 mm. diastolic was noted. The transverse cardiac measurement was 14 cm., and moist râles were present at the bases of both lungs. The liver was 4 cm. below the costal margin and tender on palpation. An electrocardiogram showed a rate of 100/min. and graphic signs of bundle branch block. She was digitalized and responded nicely. In the next 10 years she developed signs and symptoms of congestive heart failure at various times, but each time responded to renewed digitalis therapy. Repeated electrocardiograms showed a persistent bundle branch block. Finally at the age of 63 severe congestive heart failure developed, the blood pressure remained at 170 mm. Hg systolic and 110 mm. diastolic, the heart reached a size of 21 cm., and she died within three months. Eleven years after the first cardiac decompensation death occurred due to congestive heart failure.

Bundle branch block, graphically noted in this case of hypertensive heart disease, occurs in about 55 per cent of all cases.[8] It has no definite diagnostic or prognostic significance in hypertensive patients. The prognosis is that of the underlying heart condition, particularly in relation to the occurrence of congestive heart failure. The important cause of death in hypertensive patients with bundle branch block is congestive heart failure.

Case 4. C. C., a door-to-door salesman, complained of dyspnea and swelling of the ankles at the age of 55 years. He was a known hypertensive of two years' duration. On physical examination his blood pressure was 200 mm. Hg systolic and 130 mm. diastolic and the transverse cardiac measurement was 16 cm. There were impaired resonance and moist râles at the bases of both lungs, and the liver was 3 cm. below the costal margin and tender. For the next 10 years he slowly pursued his occupation, took digitalis regularly, but continued to have dyspnea on and off at various times. Repeated electrocardiograms in later years showed only a left axis deviation, except when multifocal ventricular extrasystoles appeared. At the age of 65 auricular fibrillation occurred and he was forced to discontinue work. Edema increased, he became bedridden, and died at the age of 67 of congestive heart failure.

A known hypertensive at the age of 53, this man had the first cardiac symptoms and signs at the age of 55. Twelve years after the onset of definite heart involvement he died of congestive heart failure.

Case 5. G. G., a white male continually unemployed by choice rather than by circumstances, was first found to have high blood pressure and an enlarged heart with auricular fibrillation when he complained of severe dyspnea after a heavy drinking bout at the age of 35 years. His blood pressure was 170 mm. Hg systolic and 104 mm. diastolic and the transverse cardiac measurement was 15 cm. Moist râles were present at the base of the right lung. On bed rest and treatment with digitalis the symptoms and the auricular fibrillation disappeared. During the next 10 years he complained of dyspnea on and off, depending on his omission of digitalis and degree of activity, the latter being limited except for occasional sprees. The heart size did not increase, and the blood pressure ranged between 190 mm. Hg systolic and 120 mm. diastolic and 160 mm. systolic and 100 diastolic. Digitalis would relieve the symptoms until the next time. At the age of 45 he again developed auricular fibrillation which persisted until his death two years later.

Here was a young man who had been an alcoholic for 10 years when he became acutely short of breath after a heavy spree at the age of 35. In spite of continued alcoholism he maintained good compensation with digitalis for 10 years. He died of congestive heart failure at the age of 47, twelve years after the onset of the first cardiac symptom.

Case 6. R. E., a housewife, had a hysterectomy for bleeding uterine fibroids at the age of 39 years. At the time of the operation she was a known hypertensive with the common psychic complaints of headache, dizziness, etc. Previous to surgery her blood pressure was 220 mm. Hg systolic and 160 mm. diastolic, and after the operation all her symptoms disappeared and the blood pressure decreased to 160 mm. Hg systolic and 90 mm. diastolic. Within a few months after the hysterectomy her blood pressure rose to the pre-operative level and she complained of dyspnea. The transverse cardiac measurement increased from 11 to 16 cm. Impaired resonance and moist râles were present at the bases of both lungs. The liver extended 4 cm. below the costal margin and was tender. There was moderate edema of the lower extremities. An electrocardiogram revealed a rate of 102, left axis deviation, and negative T-waves in Leads I and II. She responded to digitalis and took it regularly. Her activity was limited. After 10 years of fair compensation she began to have congestive heart failure regardless of medication. Twelve years after the onset of the hypertensive heart failure she developed a severe generalized anasarca, lingered five months in bed, and died at the age of 51 of congestive heart failure.

This was a comparatively young hypertensive who obtained complete symptomatic relief and a reduction of blood pressure from a nonspecific surgical (hysterectomy) measure.[9] Within a few months after the operation the blood pressure reached its original level and dyspnea appeared. However, she remained in fair condition for 10 years after the onset of cardiac manifestations and died of congestive heart failure.

Case 7. J. H., a card sharp, was first examined at the age of 47. He was a known hypertensive with a blood pressure of 180 mm. Hg systolic and 110 mm. diastolic, and a transverse cardiac measurement of 16 cm. There were moist râles at the bases of both lungs, and the liver was 3 cm. below the costal margin and tender. The electrocardiogram revealed a rate of 150 and left axis deviation. He was digitalized and became compensated within a week. During the next 10 years he was hospitalized 10 times during attacks of auricular fibrillation with congestive heart failure, and responded to treatment during each attack. The blood pressure varied between 125 mm. Hg systolic and 100 mm. diastolic and 100 mm. systolic and 80 mm.

diastolic during these attacks. At the age of 58 he developed a persistent auricular fibrillation, his congestive heart failure gradually became more marked and he died at the age of 59, twelve years after the onset.

This hypertensive male was seen once a year. He traveled about the country and returned to Chicago only when the symptoms became unmanageable, and had to be hospitalized. Although he always denied taking any digitalis while on the road, it was apparent each time that some of the drug had been taken in the intervals between the attacks of auricular fibrillation each year. On each occasion that he had to be hospitalized, it was for a longer period of time than in the preceding year, until the congestive heart failure no longer responded.

Case 8. L. R., a housewife, was found to have high blood pressure and a transverse cardiac diameter of 13 cm. when she complained of moderate dyspnea at the age of 61. The second aortic heart sound was markedly accentuated, and the liver was 2 cm. below the costal margin and tender. As directed, she limited her housework and took digitalis. She was dyspneic at various times during the next 15 years, but took the digitalis regularly. During this period her blood pressure ranged from 240 mm. Hg systolic and 130 mm. diastolic to 170 mm. systolic and 90 mm. diastolic. Her electrocardiogram showed a marked left axis deviation and negative T-waves in Leads I and II. At the age of 76, fifteen years after the onset of cardiac symptoms, she developed an acute coronary occlusion which was the cause of death within a week of its onset.

This hypertensive woman went along for 15 years after the first cardiac symptoms were noted and she lived long enough to develop gross arteriosclerotic changes.[7]

Case 9. M. W., a housewife, complained of dyspnea and palpitation at the age of 50 years. On physical examination she was found to have a blood pressure of 200 mm. Hg systolic and 140 mm. diastolic, a transverse cardiac measurement of 15 cm., and auricular fibrillation. Moist râles were present at the bases of both lungs, and the liver was 4 cm. below the costal margin and tender. On digitalis the auricular fibrillation disappeared and she became compensated. Later electrocardiograms showed the QRS complexes to be widened, notched and slurred. During the next 15 years she continued to have dyspnea at various times, but always responded to rest and digitalis. Her activity was always limited. Finally at the age of 66 congestive heart failure re-appeared, and three weeks before her death a left hemiplegia occurred. The blood pressure dropped to 130 mm. Hg systolic and 70 mm. diastolic, the transverse cardiac measurement was 21 cm., and auricular fibrillation was present. Death was due to a second cerebral embolus.

Sixteen years after the first cardiac manifestations appeared, this hypertensive woman died of cerebral emboli. Her first symptoms were accompanied by auricular fibrillation and this did not occur again until 16 years later at the age of 66.

Case 10. N. B., a housewife, complained of dyspnea at the age of 25. It was discovered that she had definite high blood pressure but there was no cardiac enlargement. During the next 19 years she complained of dyspnea and developed moderate edema of the ankles at various periods, but always responded to digitalis. Her greatest activity was light housework. She visited every out-patient clinic in Chicago

many times, but she was never hospitalized until five days before her death. Four or five successive generations of dispensary physicians worked her up completely, usually from a kidney standpoint. Throughout this entire period her cardiac rhythm remained regular, and the blood pressure varied from 210 mm. Hg systolic and 120 mm. diastolic to 170 mm. systolic and 110 mm. diastolic. The transverse cardiac measurement increased from 9 to 20 cm. over a period of years. Finally at the age of 44, nineteen years after the onset, she developed congestive heart failure with generalized anasarca and died in the Cook County Hospital five days after this occurred. An autopsy revealed a marked eccentric hypertrophy of the heart, which weighed 520 grams, mural thrombi in the appendage of the right auricle, passive congestion of the liver, spleen, and lungs, bilateral hydrothorax, arteriosclerotic granulation of the kidneys, and moderate atherosclerosis of the aorta.

In spite of the poor prognosis generally given a 25 year old hypertensive patient, and especially one with cardiac symptoms, this woman went along for 19 years. The arteriosclerotic granulation of the kidneys, which were shrunken considerably in size, attest to the long duration. Had this patient been subjected to any type of surgery for the lowering of blood pressure, the result undoubtedly would have been considered magnificent. Even without surgery she lived 19 years after the hypertension was discovered.

Case 11. G. C., a laborer, complained of severe precordial pain and dyspnea at the age of 34 years, at which time it was noted that he had high blood pressure. He was told that it was an attack of "acute indigestion." However, his symptoms persisted. He worked occasionally, when there was work to be had, but otherwise sat around, smoked his pipe, and lived at peace with his neighbors. For the next 20 years, until his death, he continued to complain of the same symptoms. The blood pressure varied from 210 mm. Hg systolic and 140 mm. diastolic to 170 mm. systolic and 100 mm. diastolic, and the largest transverse cardiac measurement was 18 cm. At the age of 49 he had a severe attack of epigastric pain with dyspnea. This was diagnosed as coronary thrombosis and he was kept on absolute bed rest for six weeks. After recovery, for the last five years of his life, he complained of dyspnea, precordial, and epigastric pain, and he was unable to work. At the age of 54, during an attack of acute left ventricular failure,[10] he suffered a fresh coronary occlusion and expired. An autopsy revealed a recent and an ancient thrombosis of the descending branch of the left coronary artery, an ancient organized and calcified infarct in the wall of the left ventricle, an extensive mural thrombus in the cavity of the left ventricle, eccentric hypertrophy of the heart which weighed 890 grams, multiple ancient and recent infarcts in the spleen and kidneys, liquefaction necrosis of an infarct in the spleen, moderate atherosclerosis of the pulmonary arteries, and fibrous obliteration of the pericardial sac.

Although this case was on a hypertensive and coronary basis, it is included because the coexistence of the two conditions is a common experience. The symptoms were mainly on the coronary basis, and the patient had three distinct occlusions of the coronary arteries, one at age 34, a second at age 49, and the last attack at the age of 54 years. In spite of the facts that the patient was only 34 at the time of the first attack, that he was a laborer, and that he continued at this occupation for 15 years, he lived 20 years after the initial attack but was never entirely free from symptoms. The final coronary occlusion, which resulted in his death at the age of 54, occurred during an attack of acute left ventricular failure on a hypertensive basis.[10]

Comment

These cases are of special interest from the standpoint of longevity. The first significant symptoms of cardiac insufficiency occurred 10 to 20 years prior to death. In most cases the first complaint was dyspnea. These patients were fortunate enough to escape the unpredictable and uncontrollable causes of death in hypertensives for many years. About 35 per cent of hypertensive patients do not reach the stage of severe congestive heart failure. They are carried off by the intercurrent causes of death, cerebral hemorrhage, coronary thrombosis, and uremia.

There are undoubtedly many examples of longevity with hypertensive heart disease which have not been reported. Fahr [5] cited three cases of long duration, stated that he had other cases, and that he did not believe these cases to be very exceptional. Riesman [4] stated that he had had under observation a number of hypertensive women who lived many years. In a series of 269 hypertensive heart patients, Murphy, Woods, and Grill [11] reported that only two (0.74 per cent) lived 10 years or longer after the onset of cardiac symptoms. Their high mortality may be in part explained by the fact that the patients were of the type seen in charity institutions.

The mental adjustments to heart disease are of the utmost importance. Especially is this true in hypertensive heart disease.[7] Sprague [12] made special mention of this, as one of the factors involved in disability. In the light of the factors he listed, it is of interest to analyze the 11 cases from that standpoint. Physical incapacity, the first factor, was not too great in these patients because the congestive failure was controlled by digitalis and none had the anginal syndrome. The character of the patient's work, the second factor, was important in only two cases. Six were housewives, two were unemployed, and one was a card-sharp; their work needs no special consideration. The salesman worked 10 years after his symptoms appeared, but he was his own employer and worked only enough to keep going along. The laborer worked 15 of the 20 years at a highly seasonal occupation; it is doubtful whether he worked six months of the year. Other considerations entered into the reasons why these last two patients continued to work. Both had no fear of heart disease as an incapacitating or fatal ailment. The influence of disability insurance, the fourth factor, need not be considered here as none of the patients had any policies. Disability in heart disease depends on two things: the attitude of the patient in relation to his work and activity, and the type and severity of his symptoms as related to necessary effort.

Summary

Eleven cases of hypertensive heart disease in patients who lived 10 to 20 years (average 13.7 years) after the onset of the first cardiac symptoms are reported. They were of all ages from 25 to 70 years and had various

cardiac rhythmic and conduction disturbances, neither factor apparently influencing the longevity.

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THE MORPHINE ABSTINENCE SYNDROME, ITS NATURE AND TREATMENT *

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DRUG addiction is a condition in which an individual has become sufficiently subject to an effect of a drug that he can no longer exert adequate self-control with regard to its continued use. Consequently, a separation of the patient from the drug is essential to successful treatment for drug addiction, no matter whether it has been established to opiates, marijuana, barbiturates, alcohol, tobacco, caffeine, or to any other drug or combination. The various drug addictions differ from one another in the manner and extent to which they confer tolerance, habituation, and physical dependence. Tolerance is the term used to denote the ability developed by the organism to diminish the effect of a given amount of a drug. Habituation is the term used to indicate the process of psychical conditioning to repeated effects of a drug. Physical dependence is considered to be a state in which certain physiologic processes have become so conditioned to the effects of a drug that its presence is requisite to the maintenance of homeostasis. The development of physical dependence is comparatively slow, and appears to be influenced more by the regularity and rhythmicity of administration than by the amount of the drug or the route employed.

Withdrawal signs and symptoms (referred to collectively as the "abstinence syndrome") occur when drugs are withheld from a patient who has physical dependence. The abstinence syndromes differ with each drug; for example, the abstinence syndrome which follows withdrawal of cocaine is said to consist chiefly of prolonged sleep,[1] while the outstanding manifestation of caffeine abstinence is headache.[2] The morphine abstinence syndrome, on the other hand, is usually a severe experience which may become so intense as to cause death. It reaches its peak of intensity on the second day after abrupt withdrawal and recedes slowly thereafter (figure 1), occasionally extending into the third week. If, from a "stress and strain" point of view, it is assumed that the stress of withdrawing 200 mg. of morphine is the same in each of a group of addicts, the variations in the resultant strain (abstinence syndrome) possibly reflect the degrees to which mechanisms for the maintenance of homeostasis have been affected by the drug. The severity of the abstinence syndrome varies with the intensity of the physical dependence but, as in other illnesses, may be modified somewhat by the con-

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The term "morphine" as used throughout this paper includes the phenanthrene derivatives of opium used in the practice of medicine.

dition of the patient and by his attitude. For example, the pressor effect of withdrawal will be greater in a patient with hypertension than in one with normal blood pressure. Although few patients show all of the abstinence phenomena, to be described, most of them are commonly encountered.

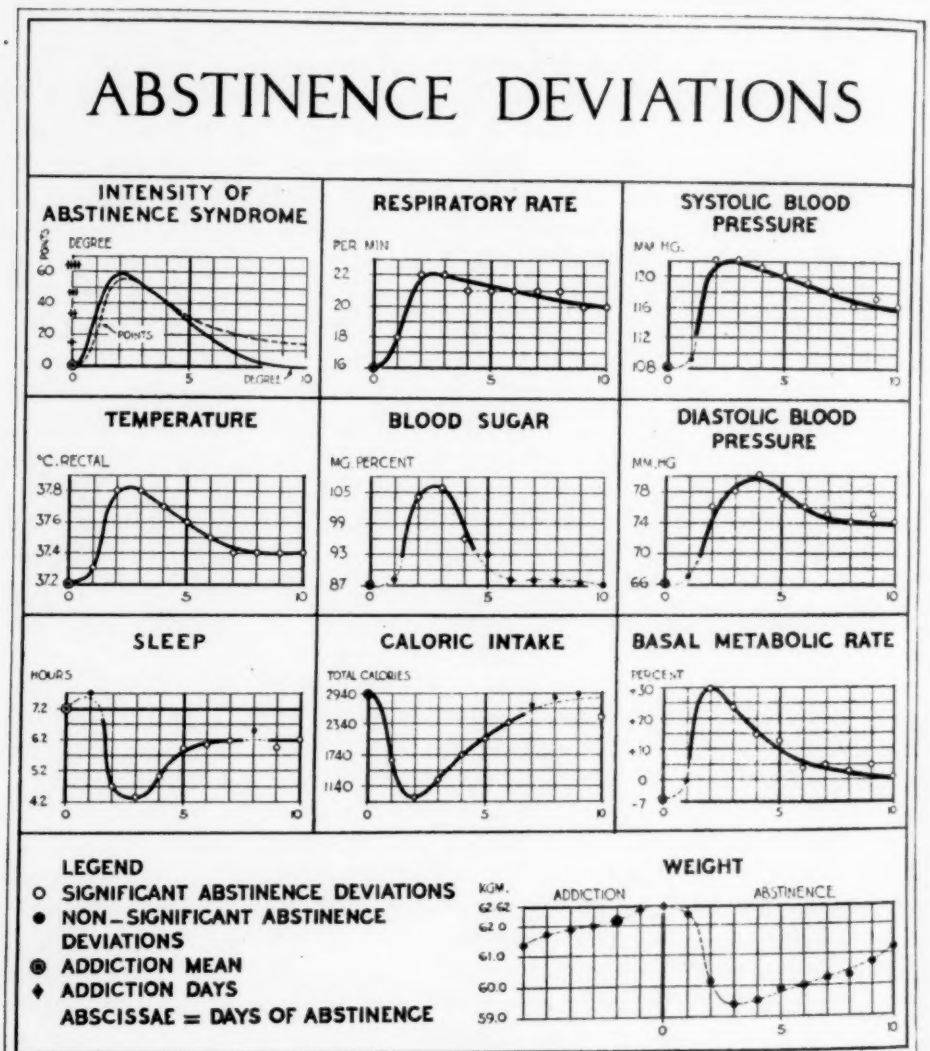

FIG. 1.

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The purposes of this article are: (1) To dispel any doubts as to the existence of an abstinence syndrome; (2) to describe the morphine abstinence syndrome; (3) to discuss simple and reasonably effective measures for alleviation of withdrawal discomfort; and (4) to emphasize that proper man-

agement of the abstinence syndrome, although essential to the treatment of drug addiction, constitutes only its first stage; hence, treatment of the abstinence syndrome should not be considered adequate treatment of addiction.

Signs and Symptoms of Abrupt and Complete Withdrawal

General Appearance. The general appearance of patients undergoes several changes during the first two weeks of abstinence. During the early part of the first day patients appear drowsy, but later in the day they seem anxious and apprehensive. They become disheveled and careless of the appearance and cleanliness of their persons and rooms. From the latter part of the second day until about the fourth day they appear sick and miserable, their posture is stooped, and they move about in a slouching, shuffling manner. When the intensity of the abstinence syndrome wanes their appearance improves, but they appear weak and tired until about the tenth day of withdrawal.

Weight. Weight is lost rapidly following withdrawal. The lowest weight, usually recorded on the second day, represents an average loss of about three kilograms (6.6 pounds). Weight is regained slowly, the addiction level not being reached until the second week of abstinence or later. The weight curve offers an indirect measure of abstinence syndrome intensity and of the recovery process (figure 1).

Eyes. The most conspicuous signs referable to the eyes are lacrimation and dilatation of the pupils. Occasionally a patient will complain of double vision. Nearly all patients, if they try to read, complain of some impairment of vision.

Ears. Patients tend to be more sensitive to ordinary ward noises following withdrawal than during addiction.

Nose. Excessive nasal secretion (rhinorrhea) is a very common sign of withdrawal. Patients sniff, snivel, and sneeze for the first four or five days of abstinence. The sneezing usually occurs in spells of three or more paroxysms at intervals of from a few minutes to several hours. Patients usually find ordinary odors offensive from the second to the fourth day of abstinence.

Tongue. Tremor of the tongue is a common withdrawal sign. The majority of patients complain of disturbed taste sense following withdrawal. For example, those who smoke usually find the taste of tobacco offensive. It is a common observation to see a patient light a cigarette, take a puff or two, exclaim over the foul taste, and throw it away in disgust. Measurements of tobacco consumption during addiction and following withdrawal, on a few patients, showed a 90 per cent reduction on the second day with a return to the addiction level by the seventh day of abstinence.

Teeth. Addicts' teeth are usually in poor condition. Toothache is more apt to be complained of following withdrawal than during addiction.

Throat. The gag reflex is usually hyperactive during the first few days after withdrawal.

Mouth. Yawning is a common sign of abstinence. It is deeper and more frequent in occurrence than the ordinary yawn of sleepiness, appears early, and continues until the fourth or fifth day of abstinence. Salivation, although rarely marked, is of common occurrence.

Respiratory System. The respiratory rate becomes accelerated following withdrawal and does not ordinarily return to the addiction level during the first two weeks of abstinence. Increased secretion of bronchial mucus is common; sputum is produced in increased amounts during the first week of abstinence. Auscultation will often reveal the presence of mucous râles not heard during addiction. Measurements of vital capacity on a few patients during addiction and following withdrawal showed no significant difference.

Cardiovascular System. Following withdrawal the heart rate may be increased, decreased, or may not deviate significantly from the rate during addiction. A patient may have bradycardia one day and tachycardia on the next. Arrhythmias have not been encountered, and no significant changes in the electrocardiogram have been found during addiction or abstinence.

The blood pressure (diastolic and systolic) rises following withdrawal. The highest readings, usually obtained on the second day, represent an average increase of 14 mm. Hg (figure 1). The blood pressure falls slowly thereafter.

Gastrointestinal Tract. Anorexia is a characteristic sign of withdrawal. Measurements of caloric intake show appetite to be poorest on the second day and to return slowly to the addiction level (figure 1). Nausea and vomiting occur in about 60 per cent of strongly addicted patients undergoing abrupt withdrawal. Vomiting may start late in the first day, and does not often persist after the fourth day of abstinence. Diarrhea is as common as nausea and emesis, usually runs the same course, and may become a major symptom. These manifestations indicate hyperactivity of the gastrointestinal tract as regards both secretion and motility. Hypermotility may be observed by auscultation; hypersecretion by the copious amounts of fluid lost through emesis and diarrhea. The vomitus often contains considerable bile. Cramps in the abdomen, alone, or accompanying emesis or diarrhea, constitute a frequent withdrawal complaint.

Skin. Gooseflesh (excessive pilomotor activity) is one of the more common signs of abstinence. It appears early in the course of withdrawal, may be transitory, and often persists into the second week of abstinence.

Patients commonly complain of generalized hot and cold flashes, predominantly cold, during the first few days of abstinence. Some patients show distinct flushing of the skin of the face and neck accompanying the "hot" flashes. However, they commonly seek added warmth; many wrap blankets around themselves in "Indian fashion."

Perspiration is another sign of withdrawal. Usually it amounts to little more than palpable moistness of the skin, but occasionally it is excessive.

Patients who have been very restless may develop abraded areas similar to the " mat burns " of wrestlers. This sign is indicative of a severe withdrawal syndrome.

Bones, Joints and Muscles. Aching referred to the bones, joints, and muscles is probably the most common symptom of withdrawal. The only sign referable to the muscles is tremor. This is seen sometimes as a fibrillary tremor, and occasionally as twitching.

Glands. Glandular activity, which has been more or less suppressed during addiction, responds to withdrawal by greatly increased secretion. This phenomenon is thought to involve the glands of internal as well as those of external secretion. The degree of glandular hyperactivity in elderly patients is not nearly so great as in younger patients. Some signs of withdrawal attributable to excessive secretion are lacrimation, rhinorrhea, salivation, perspiration, emesis, and diarrhea.

Nervous System. Anxiety, restlessness, nervousness, insomnia, and hyperreflexia are the predominant deprivation phenomena referable to the nervous system. The degree and character of anxiety, restlessness, and irritability may be influenced by a patient's personality make-up. Sleep is disturbed both in rhythm and amount, the predominant effect being on rhythm. During the first day of abstinence patients tend to sleep more than during addiction. For the next few days sleep is broken and fitful and can best be described as intermittent dozing. Inability to sleep through the night is of major concern to most patients. Sleep equivalent in amount to that of addiction is usually not regained during the first two weeks of abstinence.

Determinations of cerebrospinal fluid pressure were made on a few patients during addiction and the first week of withdrawal. All pressures were within normal limits, and no tendency to rise or fall was noted.

Electrical activity of the cerebral cortex recorded during addiction and following withdrawal has shown no abnormal rhythms.[3]

Genitourinary System. Neither the volume nor the quality of the urine (except for the presence of the drug) is appreciably disturbed during addiction. Following withdrawal, however, the urine volume falls to about 500 c.c., then rises to about 1000 c.c. by the end of the first week, but does not regain the addiction level (of about 1600 c.c.) during the second week of abstinence. At the height of withdrawal the urine is concentrated and may contain more sediment than during addiction. Increased activity of the reproductive organs occurs following withdrawal.

Metabolism. The average basal metabolic rate during addiction is minus 7 per cent. Following withdrawal the basal metabolic rate rises to an average of plus 30 per cent and then falls to zero per cent by the eighth day of abstinence (figure 1). Subsequent change is insignificant.

A low grade fever is characteristic of abstinence (figure 1). The average daily rectal temperature (at 6:00 a.m., 2:00 and 7:00 p.m.) during addiction is 37.2° C. On the second and third days of abstinence the average temperature is 37.8°, but falls slowly to 37.4° by the eighth day, and usually levels off at 37.2° during the second week.

Blood. A brief hyperglycemia of moderate degree occurs during the first week of abstinence (figure 1). Blood inorganic phosphorus drops from an average of 3.3 mg. per 100 c.c. to 2.8 on the second day, and returns to 3.0 by the tenth day of abstinence. Blood lactic acid rises from a mean addiction level of 14 mg. per cent to 45 mg. on the second day, then falls to 25 mg. by the tenth day.

The average blood sedimentation (Wintrobe tube—read at 60 minutes) during addiction is 20 mm. After withdrawal there is a small increase, but this is followed by a progressive decrease to 15 mm. in the second week of abstinence. Little change in sedimentation occurs thereafter.

Studies of blood concentration [4] showed hydration to be present during addiction. A brief relative hemoconcentration occurs during the early part of abstinence; following this the blood becomes hydrated again before returning to normal.

Leukocytosis has been reported to occur following withdrawal,[5] but observations made at this hospital have failed to show a significant increase in leukocytes.

Comment

The signs and symptoms of withdrawal indicate that the morphine abstinence syndrome constitutes a very real and characteristic illness. Although several of these deprivation phenomena can be modified by psychical influences, it is certainly unlikely that this syndrome is entirely psychogenic. The term " functional " can be applied to the abstinence syndrome *if* this word is used in the sense that the deprivation phenomena represent derangements of normal action without demonstrable structural alterations.

In certain of its aspects the abstinence syndrome resembles hyperthyroidism, in others, water poisoning [6]; but a more likely cause would appear to be a disturbance affecting the autonomic division of the nervous system, possibly localized in the hypothalamus. Grinker and Serota [7] found that excitation of the hypothalamic region in man caused rise in blood pressure, dilatation of the pupils, perspiration, and hyperemia of the skin. Elevation of blood pressure, dilatation of the pupils, hyperpnea, gooseflesh, and hyperglycemia can be cited as examples of sympathetic hyperactivity. On the other hand certain abstinence phenomena, such as increased activity of the glands and of the gastrointestinal tract, can be regarded as examples of hyperactivity of the parasympathetic portion. An increased liberation of acetylcholine and/or an inhibition of cholinesterase could account for manifestations of hyperactivity of both portions of the autonomic division, for acetylcholine stimulates ganglia as well as parasympathetic endings.

Treatment of the Abstinence Syndrome

Although the majority of addicts find psychic satisfaction in morphine, many resent physical subjection to its powerful influence. This resentment causes them to want treatment, but, since they dread the discomforts of withdrawal, procrastination is characteristic.

It might be assumed that any person who abuses an opiate necessarily develops strong physical dependence upon it; however, although habituation and tolerance seem to develop with comparative ease, physical dependence of truly strong intensity is found in only 20 to 25 per cent of addicts admitted directly to this hospital. One reason for this is thought to be that the adulteration and expense of illicit drugs result in the addict's getting weaker drugs at less regular intervals than are consistent with the development and maintenance of strong physical dependence. As a matter of fact, reduced and irregularly spaced doses of morphine constitute the basis for the better methods of withdrawal treatment.

Accordingly, it seems that the presence of marked or strong physical dependence should be established prior to starting treatment for it. This can be accomplished easily by withholding opiates until signs of withdrawal appear. When the presence of marked or strong physical dependence has been demonstrated, the patient should be temporarily stabilized on the minimal amount of morphine required to prevent withdrawal signs prior to completion of the withdrawal. The amount of morphine required for "stabilization" is usually one and one-half to three grains per day, sometimes four, occasionally more. The total daily dose should be divided into four equal amounts administered subcutaneously. A satisfactory injection schedule is: 6:00 and 11:00 a.m., and 5:00 and 10:00 p.m. Usually before the third day on this program patients will be in satisfactory physical equilibrium. If no serious physical disease exists, the period of stabilization need not exceed one week. During this period history, physical examination and any special examinations can be completed and the decision made as to whether or not further withdrawal can be accomplished safely. Then, too, withdrawal should not be completed until coexisting diseases which might endanger the patient's life (e.g., pneumonia, cardiac decompensation) are either cured or brought under adequate control. This period also gives the patient an opportunity to adjust to the hospital routine and to gain confidence in his physician and nurses.

It is convenient to give the last regular dose of morphine at 10:00 p.m., and it is usually better to avoid letting the patient know when this is to be done. Patients should not be led to believe that withdrawal will not entail discomfort.

The purpose of withdrawal treatment is to relieve the patient of physical dependence safely, yet without undue suffering or prolongation of treatment. Since ambulatory and home treatments are unsatisfactory as a rule, withdrawal should be attempted in a hospital. Many so-called "specific" treat-

ments have been developed, but often these do more harm than good.[8] The only true " specific " for alleviation of phenomena caused by withdrawal is morphine or one of its derivatives. The effect of one " stabilization " dose of morphine on the abstinence syndrome is shown in figure 2. The difference in the areas (A. S. I. point-days) within the mean withdrawal curves of the groups of untreated and treated patients for the first five days shows a reduction of 22 per cent in the treated group. Excessive use of morphine will, of course, tend to prolong unnecessarily the abstinence syndrome by giving partial support to the addiction process.

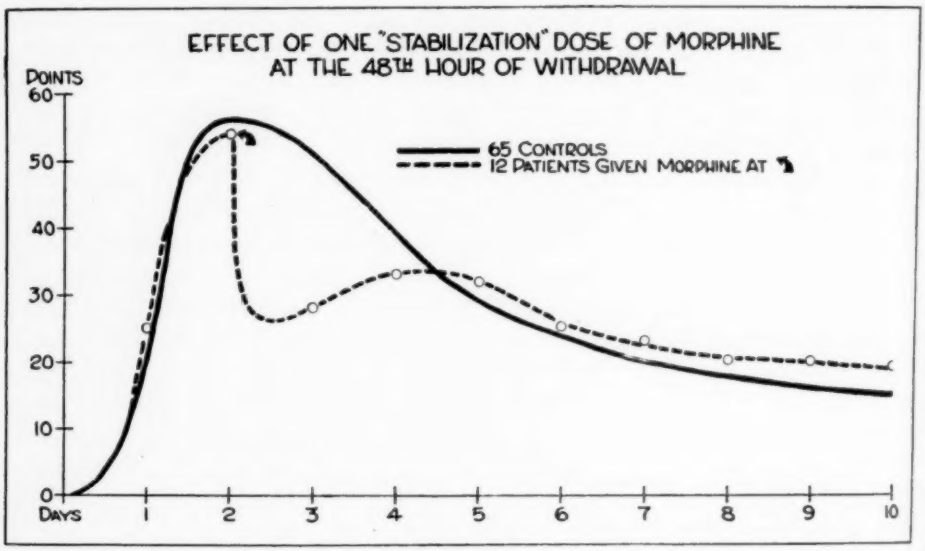

FIG. 2.

Withdrawal should be rapid rather than abrupt or slow. A fixed, prearranged schedule of opiate medication has certain advantages over a haphazard method, but should be modified upon appropriate clinical indication. A satisfactory schedule is to give an injection of morphine at every third stabilization dose interval for three days, reducing the size of each subsequent dose. For example, if the patient was stabilized on one grain of morphine four times a day prior to withdrawal, give one grain of morphine at 5:00 p.m. on the first day, three-quarters of a grain at 11:00 a.m., on the second day, one-half grain at 6:00 a.m. and one-quarter grain at 10:00 p.m. on the third day. No morphine need be given thereafter, but substitution of codeine for morphine on a similar schedule (figure 3) will facilitate recovery. These doses and intervals of opiate administration are consonant with the durations of physical dependence action of morphine and codeine, and of effective withdrawal.

On the second and third days following withdrawal, bromides in amounts up to 60 grains three times daily are given to reduce the intensity of nervousness and restlessness. The administration of bromides should be restricted to two days and the sodium chloride intake should be adequate.

Insomnia due to marked restlessness and nervousness has been found to respond better to the administration of paraldehyde than to other hypnotics. Barbiturates for example tend to cause addicts undergoing withdrawal to become confused and delirious.[9] Ten to 15 cubic centimeters of paraldehyde

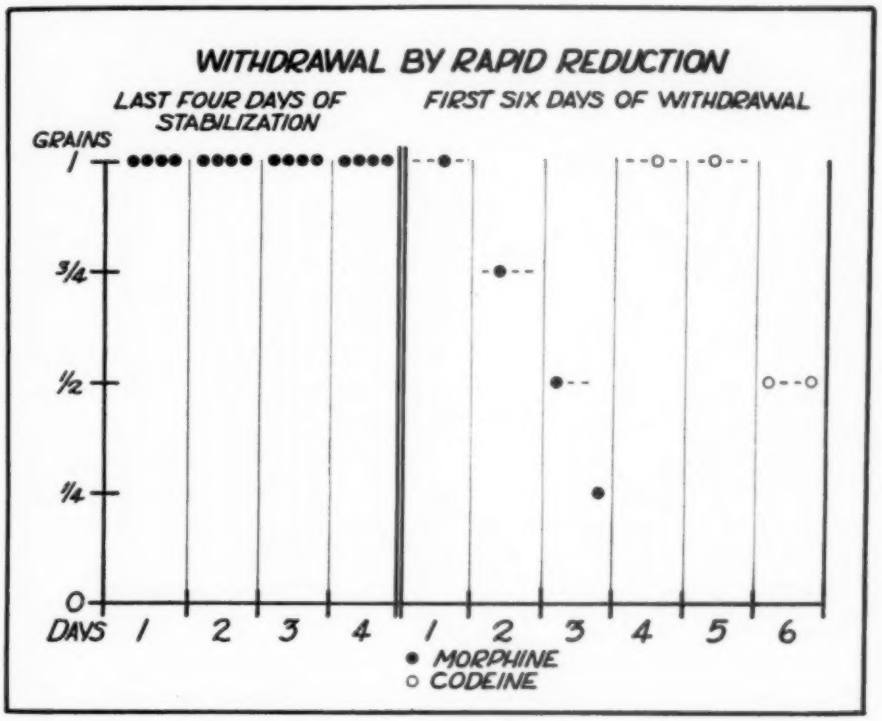

FIG. 3.

(with 50 to 60 cubic centimeters of warm olive or cotton seed oil) are administered per rectum, after a low cleansing enema, on the second or third night after withdrawal. Sedative flow baths also are effective in reducing restlessness and should be given twice daily on the second, third and fourth days of abstinence. The following technic has proved satisfactory. The patient is placed in a tub filled with warm water (98° F.). The water temperature is slowly increased (over a period of 10 minutes) to 102 to 104° F. This temperature is maintained for three to five minutes, then in the next five minutes it is reduced to about 80° F., and the patient is then removed. If the pulse rate goes over 110, or if the patient becomes faint, the temperature of the water should be reduced promptly and the patient removed.

Flow baths and massage will often relieve aches and pains in the legs and back. Massage is more often effective when given directly after a flow bath. Aspirin (five grains) every two or three hours also reduces the intensity of these complaints. Sometimes codeine (one-half grain) by mouth is necessary to relieve severe aches and pains.

Intravenous infusions are given on the second, third and sometimes the fourth days of withdrawal in order to restore the fluid and salt losses. One liter of 0.85 per cent NaCl or of Ringer's solution is given before noon, and one liter of 5 per cent or 10 per cent aqueous solution of dextrose in the even-

TABLE I

Point System for Measuring Abstinence Syndrome Intensity by the Day (D) or by the Hour (H)

	By Day (D)		By Hour (H)	
	Points	Limit	Points	Limit
Yawning	1	1	1	1
Lacrimation	1	1	1	1
Rhinorrhea	1	1	1	1
Perspiration	1	1	1	1
Mydriasis	3	3	3	3
Tremor	3	3	3	3
Gooseflesh	3	3	3	3
Anorexia (40 per cent decrease in caloric intake)	3	3	—	—
Restlessness	5	5	5	5
Emesis (each spell)	5	—	5	5
Fever (for each 0.1° C. rise over mean addiction level)	1	—	1	10
Hyperpnea (for each resp./min. rise over mean addiction level)	1	—	1	10
Rise in a.m. systolic B. P. (for each 2 mm. Hg over mean addiction level)	1	15	1	10
Weight loss (a.m.) (for each lb. from last day of addiction)	1	—	—	—

Total abstinence syndrome intensity score per day or per hour is the sum of the points scored in the (D) or (H) columns, respectively, with due attention to the limits.

ing. It has been found that greater subjective relief is obtained when infusions are given rapidly (15 to 20 minutes) and at room temperature.

Ice collars are used to reduce nausea. Small doses of a short-acting barbiturate (e.g., one grain of "Ipral") often reduce the severity of gastrointestinal symptoms. Diarrhea, if left unchecked, may become distressing, but can be controlled by bismuth subcarbonate in 15 grain doses repeated three or more times daily on the second, third and fourth days of withdrawal.

Liquids, such as eggnog, milk, and fruit juices are usually tolerated by patients during the first two or three days of withdrawal. Later the liquid diet is replaced by a soft diet, consisting of easily assimilable foods. Patients usually ask for a full regular diet by the fifth to the seventh day.

The attitude of the nurse should be sympathetic and reassuring, yet gently firm. Attention must be given to the minor as well as the major comforts

of the patient. Frequent changes of bed linen and pajamas and the maintenance of neatness and cleanliness are greatly appreciated by patients undergoing withdrawal.

Recorded observations of temperature, pulse, respiration, blood pressure and all withdrawal signs should be made at least every two hours (when the patient is awake) on the first day, hourly on the second day, and three times daily thereafter through the tenth to fifteenth day of abstinence. The patient should be weighed at the same time each morning. With such data the intensity of the abstinence syndrome can be evaluated with sufficient accuracy to follow the progress of the patient adequately and to permit valid comparisons of one form of treatment with another. The objective abstinence phenomena have formed the basis of systems for scoring the intensity of the abstinence syndrome. The system now in use at this hospital is summarized in table 1.

Summary

The morphine abstinence syndrome is a definite clinical entity. Some of the more common signs and symptoms of this syndrome are: yawning, lacrimation, rhinorrhea, perspiration, gooseflesh, tremor, dilated pupils, nervousness, restlessness, aching of legs, anorexia, nausea, abdominal cramps, emesis, diarrhea, insomnia, fever, hyperpnea, elevation of blood pressure, and loss of weight. An adequate program for management of the abstinence syndrome consists of a preliminary period of stabilization, rapid reduction of morphine, harmless supplementary measures such as infusions, sedatives, and flow baths, and good nursing with frequent and careful observation. The most important feature of withdrawal treatment is the judicious use of opiates.

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THE LOCAL AND REGIONAL INJECTION TREATMENT OF LOW BACK PAIN AND SCIATICA *

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The origin of the local and regional injection treatment of low back pain and sciatica dates back to the earliest descriptions of acupuncture. In the Tsin period around 300 A.D. appeared Huang Fu's classical treatise describing the method of treating painful lesions by the insertion of long needles into the subcutaneous or muscular structures. Churchill's monograph in 1821 reviewed the subject of acupuncture historically, described the technic and presented cases of thoracic and lumbar pain in which it had been used with success. In 1828 a second article gave in detail its use in many additional cases of rheumatism, lumbago, and sciatica. Similar experiences were recorded by many observers who inserted needles deeply along the course of the sciatic nerve. Fayrer described direct puncture of the nerve sheath with relief of tension.

More recently, injection of the sciatic nerve trunk and its surrounding tissues with anesthetic solutions, quinine and urea, chloroform, alcohol, osmic acid and other substances has been a popular method of treatment. The injection of oxygen into the perineural interstitial spaces was suggested by Cordier in 1902. Epidural injection of novocaine, salt solution, camphorated oil, magnesium sulfate, iodized oil, Ringer's solution, oxygen, antipyrine and liquid petrolatum have been widely used with varying results, following the original descriptions by Sicard and Cathelin in 1901. Babcock noted the use of warm water or 2 per cent phenol injected into the muscles of the back in cases of lumbago. Hertzler stated that older authors treated low back and sciatic pain by the injection of morphine into the quadratus lumborum muscles or the painful points along the sciatic nerve. Simple spinal puncture, and intraspinal injections of procaine and alcohol have been recommended in the treatment of sciatic pain.

In the last few years numerous articles have appeared in the literature describing the beneficial effects of injections of various substances into varying anatomic locations, all with the express purpose of relieving low back and sciatic pain, each with a different approach and an individual rationale, but all with amazingly uniform successful results. There is no consistency of substance injected, location attacked or modus operandi, but the type of patient treated is relatively uniform, each observer finding to his own satisfaction a logical explanation for the reported success. The reports are as

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confusing as our present knowledge of the etiology and mechanism of low back pain and sciatica, and evaluation is urgently required if the method is to be retained as a rational form of treatment.

The work of Carnett in 1926 in the diagnosis of intercostal and first lumbar neuralgia and in its differentiation from intra-abdominal and intrathoracic pain is outstanding as an early influence in the presently favored method of injection for the relief of low back pain. For diagnostic purposes anesthetization of the posterior divisions of the intercostal and first lumbar nerves produced relief of pain and tenderness along the peripheral distribution of these nerves. In 1931 Labat and Greene noted relief of pain by injection of weak solutions (1–3) of 95 per cent alcohol in 1 per cent novocaine into tender areas of the back which were determined by means of a percussion hammer. They found the second and third lumbar and the first sacral areas to be the ones chiefly involved.

Following the work of Carnett, Judovich and Bates observed that many cases of low back pain were due to irritation of the posterior divisions of the twelfth dorsal and first lumbar nerves, with pain and tenderness along the cutaneous distribution of these nerves in the upper gluteal area and, anteriorly, in the groin and upper, inner thigh. They stated that many cases thought to be suffering from sacroiliac and lumbosacral strain were in reality twelfth dorsal and first lumbar neuralgias with referred pain and tenderness along the peripheral distribution of these nerves. Temporary relief was obtained by injection of a procaine solution around the points of emergence of the nerves from their foramina, and permanent relief was often obtained by a combination of procaine and an aqueous extract of the pitcher plant. Irwig injected an area in the lower back midway between the fifth lumbar spinous process and the iliac crest for low back and sciatic pain. He first used 1 per cent procaine, but later recommended a solution of 1 per cent eucupin in oil because of the more permanent effect. Tarsy reported the use of an anesthetic in oil injected into the tender areas of the lower back. Steinbrocker injected a 2 per cent solution of procaine in oil paravertebrally.

Steindler and Luck in 1938 reported the use of procaine solution as a diagnostic agent in low back pain and sciatica. In many cases thought to be due to irritation of the posterior divisions of the spinal nerves, injection of the most tender area of the lower back or buttock produced first an exaggeration of the back and leg pain. With the injection of the solution, the pain and tenderness in the back and leg subsided and previously positive leg signs disappeared. When relief was obtained by injection this was considered as proof of the local site of pathology and of the reflex nature of the sciatic pain. Kellgren noted that pressure on tender points in lumbar myalgia and fibrositis often produced referred segmental pain. This could also be produced by injection of the area with novocaine or salt solution. Novocaine usually gave relief of signs and symptoms and often abolished them entirely.

Gorrell and Copeman reported successful results in lumbago due to fibrositis with the use of nupercaine injection of the tender areas of the lower back. Russetzki, Teneff and Walker used periarticular and intramuscular injections of novocaine. Haggart reported the use of 1 per cent novocaine injected in quantities of 150 c.c. around the sciatic nerve at its exit from the notch in cases of sciatica of unknown origin. Haldeman and Soto-Hall injected 20 to 30 c.c. of 1 per cent procaine into the posterior sacroiliac ligaments in sacroiliac lesions with immediate disappearance of signs and symptoms in almost all of their cases. Douthwaite mentions acupuncture as a method of treatment for sciatic pain, and Bring and Goulden have reported successful results with this method used along the course of the sciatic trunk. The latter observer conducted a galvanic current through the needle.

Injection of procaine directly into the substance of the pyriformis muscle is used by Kreuz with startling relief of symptoms of low back pain and sciatica. Gratz, believing that many cases of low back and sciatic pain were due to myosynovitis and adhesions within the fascial planes of the back, buttock and thigh, used insufflation of air into the fascial spaces with considerable success. Forestier used iodized oil which he injected into the local points of tenderness. Copeman suggested that in many cases simple needling of tender areas of the lower back was sufficient to relieve local and radiating pain. In a consideration of the relief of somatic pain by anesthetization, Allen and Tuohy question whether it is the solution or the injection which is responsible.

Galland injected 0.2 to 0.4 c.c. of a 2 per cent alcoholic iodine solution into the posterior aspect of the sacro-iliac joint with relief of discomfort in cases of low back pain. Harris and Verrall described a case of low back pain and sciatica relieved instantly by injection of alcohol deeply into the tender area behind and below the fourth lumbar transverse process. Thomson injected ½ to 1 c.c. of thiosinamine compound into the tender nodules of the back in cases of lumbago with good results. Tolderlund recommended the use of intramuscular injections of formic acid. Mayers and Livingston injected a formic acid, sulfur, iodine, camphor preparation into the tender lumbar areas. Smyslov recommended the intramuscular injection of distilled water and hypotonic salt solution into the areas of referred pain.

The questions immediately arising may be stated in the following manner: What is the etiology of the low back and sciatic pain which is relieved temporarily or permanently by the injection treatment? What is the chemical or physical action of the substances injected? What is the significance of the area selected for the injection in any particular case? Is there a psychic factor involved in the success of the injection treatment? And finally what are the definite uses and limitations of this rapidly growing form of therapy?

In an attempt to convince ourselves of the efficacy of this form of treatment in the routine case of low back and sciatic pain, an unselected series of

70 consecutive patients was thoroughly studied. The examination consisted of a detailed history, complete orthopedic examination including the use of a considerable number of the accepted diagnostic tests, comprehensive radiologic examination of the pelvis and spine, and urine and blood examinations. All patients had nose and throat and dental examinations, the females had gynecologic studies and the males urologic examinations. Those presenting neurologic signs were studied in association with a neurologist, and lumbar puncture and lipiodol studies or air myelograms were performed when indicated. There was no selection of cases except that those presenting conditions obviously requiring surgery or cases in which the back pain was symptomatic of gynecologic or urologic conditions were not subjected to the injection treatment nor included in the series. The patients were a typical group presenting themselves for treatment for concededly orthopedic conditions resulting in low back and sciatic pain.

Method of Treatment

After detailed study to eliminate those patients who might have definite requirements for other forms of treatment, there remained 62 patients who we felt were suitable. The paraspinal intramuscular method of injection was used and the patients were divided into three groups. The first group of 28 cases received 10 to 15 c.c. of 1 per cent novocaine injected into the lumbar muscle mass, unilaterally or bilaterally, depending upon the nature of the complaint. The needle was inserted at a point two inches lateral to the spinous process and directed at a 45 degree angle with the skin toward the posterior division of the lumbar nerve at its exit from the foramen. Injection directly into the nerve was not considered essential. The areas of injection varied, the initial injection being made opposite the first lumbar spinous process, the second opposite the second lumbar and so on down to the fifth. If further injection was required, the next injection started again at the first lumbar area. Only one area was injected at the time of each treatment and injections were given at weekly intervals. This routine was continued regardless of the exact location of the patient's complaints or the type of radiating pain. On numerous occasions it was felt that the first thrust of the needle did not locate the region of exit of the lumbar nerve so that the needle was partially withdrawn and re-inserted. Therefore, there was often a multiple puncture of the fascia and muscle at the time of the individual injection.

The second group of 17 patients was injected in a similar manner but with 10 to 15 c.c. of normal salt solution. The third group was similarly treated by the insertion of a 2½ inch, 22 gauge needle into the same series of locations, but nothing was injected. The total number of injection treatments was 231. Because some of these were bilateral, the total number of injections was 338. In the individual cases the number of injections varied between one and eleven, the average per patient being 3.7. At no time dur-

ing the course of the injection treatment was any other therapeutic measure employed for the relief of the low back and sciatic pain.

Clinical Data

There were 44 females and 18 males. The ages varied between 17 and 73 years. There were three patients in the second decade, seven in the third, 14 in the fourth, 24 in the fifth, eight in the sixth, four in the seventh and two in the eighth. The duration of symptoms varied between one week and 20 years. Three cases were of less than one month's duration, nine were between one and five months, three between six and 11 months, and 47 existed for a year or more. A definite functional element was present in 21 of the patients. The radiologic findings included lumbosacral anomalies in 29 cases, hypertrophic arthritis in 39, atrophic arthritis in two, sacroiliac osteochondritis in one, kyphoscoliosis in 18, and posterior displacement of the fifth lumbar vertebra in four. In four cases the radiograms were normal. A more detailed account of these findings in comparison with a series of painless backs is being reported elsewhere. Referred abdominal or leg pain was present in 27 cases. A history of trauma in relation to the onset of back pain was noted in only eight cases.

Clinical Diagnosis

The diagnoses were based on the histories, physical findings and the results of the radiograms and special examinations. There was no direct relationship between the clinical diagnoses and the areas in the radiograms showing the most marked abnormality. The diagnoses were made under two classifications, according to the area involved and to the type of pathology thought to exist. Thirty-two patients had lumbar lesions, 13 lumbosacral, three dorsolumbar, nine sacroiliac and five had combined areas of pathology. In 41 patients, strain or myofascitis was thought to be the underlying cause, in 14 hypertrophic arthritis, in one protrusion of a disc, in one osteochondritis and in five a combination of causes.

Results

The end results were divided into three groups: those with no relief, those with permanent relief and those with temporary relief. By permanent relief is meant at least a full year with absent or markedly decreased complaints. Table 1 represents the results of the injection treatment. In the entire series of 62 cases, 35 (56 per cent) obtained some type of relief. Permanent relief was obtained in 18 (29 per cent).

In the novocaine series, 16 (57 per cent) obtained some type of relief. In 12 (43 per cent) this relief was permanent, whereas in four (14 per cent) the relief was temporary. In the salt solution group, nine (53 per cent) obtained relief. Two (12 per cent) obtained permanent relief, whereas in

seven (41 per cent) the relief was temporary. The use of the needle alone produced some type of relief in 10 (59 per cent). Of these, four (24 per cent) were permanent and six (35 per cent) were temporary.

TABLE I
Type of Relief

	Cases	Permanent		Temporary		Any Type
		Complete	Partial	Complete	Partial	
Novocaine	28	5 (18%)	7 (25%)	0	4 (14%)	16 (57%)
Salt Solution	17	1 (6%)	1 (6%)	4 (24%)	3 (17%)	9 (53%)
Needle	17	2 (12%)	2 (12%)	1 (6%)	5 (29%)	10 (59%)
Total	62	8	10	5	12	35 (56%)

Analysis of Results

Similar proportions of our patients obtained relief in each of the three groups. The novocaine group presented a definitely higher percentage of permanent relief than either of the others, so that the type of fluid injected may have some bearing on the results. The considerable success with the needle alone, however, is somewhat startling in this respect. Simple relief of tension may be a factor in the relief obtained. Disruption of adhesions by the injected solutions may be a factor but good results were obtained by the needle alone.

The successful cases were analyzed in relation to the results previously obtained by other forms of treatment. All of the 18 cases which obtained permanent relief had had no similar relief from other forms of treatment which included rest, oral and parenteral medication, support, physiotherapy and forms of manipulation. Of the 17 cases with temporary relief, four had had similar relief by other treatment and one patient had comparable reduction of pain from time to time without treatment of any kind.

The results were studied in relation to the emotional state of the patients in the group which obtained relief. Of the 18 patients who obtained permanent relief, 13 were considered normal in this respect, and in five there was a definite neurotic element. The novocaine cases presented a definitely higher percentage of normals in this classification (10 of 12 cases). In all of the eight cases with complete permanent relief, the patients were considered normal. Of the 17 patients with temporary relief, about half were neurotic and the same proportion existed in each of the three injection groups.

It would appear from the comparison of the results with the reaction to former treatment and the emotional type of the individual, that the psychic factor is not of major importance. These patients had considerable opportunity to be impressed by previous forms of treatment including subcutaneous and intravenous medication. The emotional make-up was esti-

mated before the effects of the treatment were known or suspected. The best results were obtained in individuals thought to present an insignificant functional element in their complaints.

The duration of complaints was apparently of tremendous importance in the percentage of successful results. Of 15 patients with complaints of less than one year's duration, 14 were relieved, nine permanently and five temporarily. The one case of short duration which was not benefited was in the salt solution group. Of 47 patients with a duration of complaints of a year or longer, only 21 obtained any form of relief. There were proportionate failures in all of the three injection groups. It would seem then, that in the early cases there is a much better chance for relief by the injection treatment and the type of injection used is again of little importance. It must be noted, however, that the novocaine injections provided a higher percentage of permanent relief.

Comparing the successful results with the clinical diagnoses revealed little difference in the effect of the injections in relation to the type and area of the lesion. In regard to the area of the lesion, there was apparently no difference in the results of the injection treatment. Proportionately good results were obtained in all of the involved areas. In the type classification there was, similarly, some relief in all of the pathologic groups except the protruded disc and osteochondritis. It should be noted, however, that in the 18 cases with permanent relief, 12 were thought to be due to strain or myofascitis, and in the eight cases with complete permanent relief, all except one (hypertrophic arthritis) were in that category.

The results were analyzed in relation to the area of injection in an attempt to determine the importance of the site injected. The cases were here divided into two types: those which had injection only into the first, second and third lumbar areas, and those in which all of the lumbar areas were injected. There were no cases in which the fourth and fifth lumbar areas alone were treated. In general the effects were similar in the two types. In the novocaine cases, the results seemed somewhat better in those in which the upper lumbar areas alone were injected. This was even more definite in the cases which obtained permanent relief.

An analysis of the individual reactions to each injection bears out this impression that the site of injection is of no great importance in determining the results. A similar proportion of patients was benefited by the injections in each of the five lumbar areas. This bears no relation to the final results but seems to favor the non-specificity of any single area of the lumbar region as the site of injection. The effect is that reported by the patient when seen subsequent to the individual injection (table 2).

At the time of injection pain radiated to various areas. In 23 cases it was felt chiefly in the lumbar area, in one case principally in the buttock, in five cases the lumbar region and buttock, in seven cases the lumbar region, groin and anterior thigh, in eight cases in the sciatic distribution and in 18

cases in both the lumbar region and the sciatic distribution. The depth of the injection produced varying effects. In some cases deep injection produced only local pain. In others, radiation of pain was felt while the needle was still superficial to the transverse processes. The pain at the time of injection was not necessarily a reproduction or exaggeration of the patient's original pain. In most cases the complaints and the radiation of pain on injection were dissimilar. The successful cases showed no constant type of radiation of pain on injection, and in these cases there was no relationship between original pain and pain on injection. All locations of radiation were represented in the patients with temporary or permanent relief.

TABLE II
Individual Relief from Each Injection

		Relief	Questionable	None	Total
Novocaine	1 L	12	12	17	41
	2 L	12	5	15	32
	3 L	10	5	5	20
	4 L	8	4	4	16
	5 L	2	1	3	6
Salt Solution	1 L	6	6	11	23
	2 L	4	5	7	16
	3 L	5	2	6	13
	4 L	3	3	3	9
Needle	1 L	7	4	10	21
	2 L	8	4	4	16
	3 L	6	4	2	12
	4 L	2	3	1	6
Total		85	58	88	231

While most patients complained of pain on injection at a certain area regardless of the site of injection, there were many cases in which different areas of radiation were noted following individual injections. In these latter cases, however, there was no definite pattern of radiating pain produced by the injection of any specific lumbar area. A similar proportion of injections in each of the five areas produced sciatic pain. The same was noted in the production of groin and anterior thigh pain.

Of the 35 successful cases, 10 obtained relief of discomfort immediately or within an hour after injection. In four cases, the relief came in several hours and in 21 no improvement was noted for several days. In general each patient noted relief in a similar period of time after each injection, the exceptional case varying in the time in which relief was obtained. In the successful cases, not every injection was followed by relief, and in the failures, many injections were followed by temporary relief with early recurrence. Thus, of 231 injection treatments, 85 were followed by definite relief, 58 by questionable relief and 88 by no relief.

In the entire series of 62 cases, the immediate effects of the injections on the physical signs consisted of relief of tenderness in 10 cases, improved spinal motion in six cases, improved straight leg raising in two cases, change in Gaenslen sign in one case and change in Ober sign in one case. The relief of tenderness occurred in the novocaine group in eight cases, in the salt solution group in two and from the needle alone in none. The other effects were distributed evenly in the three groups. The Gaenslen and Ober sign changes occurred in salt solution cases.

The signs at the time of the patient's last visit in the successful cases revealed improvement in spinal bending and relief of pain on motion in 18 of 35, decreased tenderness in 17 of 35, improvement in straight leg raising in 7 of 10, loss of Gaenslen sign in 3 of 4, loss of pain in fabere test in 3 of 4, and relief of pain on internal rotation of the hip in two cases. In the failures there was no significant change in the physical signs despite reported temporary relief after various individual injections.

Comment

It is not the purpose of this paper to discuss the varied etiology, the poorly understood mechanism or the general therapeusis of low back and sciatic pain. The analysis of the present series, however, may be of service in evaluating the rationale, indications and limitations of the injection method of treatment. The etiology of our successful cases included those due to strain, myofascitis, hypertrophic arthritis, atrophic arthritis and a combination of these factors. Ligamentous, articular, muscular and intermuscular causes of pain would appear to be those best suited to the injection treatment. It is possible that in patients with other basic causes, as for example intraspinal or bone lesions, there are associated ligamentous or muscular changes which may be somewhat improved by the injection treatment. In any discussion of this type of treatment it must immediately be understood that we are dealing with symptomatic therapy, and that, whenever possible, the basic cause of the ligamentous, articular, muscular or intermuscular abnormality should be detected and removed.

The location in the lower back or buttock of the pathologic process responsible for the back and leg pain seems to be of no great importance so far as the efficacy of the injection treatment is concerned. This suggests at once the possibility of mistaken diagnosis and this criticism is not unwarranted. It is possible to be misled by an area of referred tenderness so that a primary lumbar lesion may be thought to be sacroiliac or gluteal in origin. We do not believe, however, that all of our successful cases were due to lumbar lesions. It is possible that the effect is that of relief of a secondary area of pathology or of muscle spasm in the area which is injected.

The mechanism of the relief of discomfort is still problematical. The functional element has been fairly well eliminated. From the various substances which have been used by other observers with considerable success

and from our own experience, it would seem that there is one and only one common factor in all of the cases which have been relieved by the injection treatment and that factor is the needle.

The theories quoted by others for their successful results which include effects due to the production of hyperemia, regional shock therapy, interruption of sensory reflex, restoration of vasomotor equilibrium, altered local tissue metabolism or stretching of adhesions would seem fantastic in the light of results obtained by the needle alone. The relief of increased intramuscular or intrafascial tension and edema, or the reduction of muscle spasm, as has been suggested, might, however, offer a reasonable explanation of symptomatic improvement. That this should, in some of our cases, be followed by permanent relief of symptoms and improvement in physical signs is no more readily explained than similar effects reported by others with the use of a host of varying substances.

The site of injection apparently bears no definite relation to the success of the treatment and is not necessarily directly connected with the location of the causative lesion. Patients have been relieved by injection of epidural, intermuscular and perineural spaces, posterior divisions of the lumbar nerves, muscular and nervous tissues and the subarachnoid space, and the injections have varied in location from the lower dorsal region to the lower thigh. In our own series the individual responses of relief obtained and the successful end results were independent of the particular area of the lumbar region which was injected.

The radiation of pain at the time of injection in both the failures and the successful cases bore no relationship to the original complaints. Furthermore, the depth of injection was not constant in the production of radiating pain. The area of injection provoked no constant type of radiation. These observations suggest again the non-specificity of the injection treatment as to location of the causative factor and as to the area at which the injection is made. They further suggest that there is no definite relationship between the area of the causative lesion and the type of radiating pain.

Provided that injections are made under aseptic technic and provided that no harmful or unduly irritating substance is injected, there are no contraindications to the injection treatment. Carelessly used, however, the method is bound to be the cause of faulty diagnosis, delay in adequate treatment and unduly prolonged convalescence. Penetration of the subarachnoid space by the needle must be avoided. The treatment must be recognized as symptomatic and the basic factors tracked down and eradicated. The method should be used only in patients who have had the benefit of a complete physical examination, radiologic studies and the elimination of remote causes of low back and sciatic pain. It should not be used in osseous, intraspinal, pelvic and genito-urinary causes of pain. It should not be used as a shotgun procedure in the case of any patient presenting these complaints. It should not be used as a method of psychotherapy. It should not be used, except as

a temporary measure for the relief of pain, in bone and joint lesions which suggest the application of another form of treatment calculated to influence the *cause* of the complaints.

Conclusions

1. The local and regional injection treatment of low back and sciatic pain is a symptomatic treatment which must be accompanied by measures to alleviate or eradicate the cause of the disorder.

2. The treatment offers a possibility of success in cases where discomfort is due to muscular, ligamentous, articular or intermuscular causes.

3. The functional element is of no importance in the success of the injection treatment.

4. The treatment offers better chance for success in the cases of short duration.

5. There is no specific area of the back or buttock in which the injection should be made and the area of injection bears no definite relation to the site of the causative lesion.

6. There is no specific palliative or curative substance or solution to be injected.

7. There is no logical explanation at hand for the temporary and permanent relief which has been obtained. Relief of intramuscular and intermuscular tension, and diminution of muscle spasm are the most reasonable explanations but there is no available proof.

8. The observation that the common factor in the success obtained by various observers with a host of substances in widely varying anatomic locations is the use of a needle, suggests the ancient therapeutic procedure of acupuncture.

Summary

1. The history of the local and regional injection treatment of low back and sciatic pain is reviewed.

2. A series of 62 consecutive patients treated by this method is presented. All cases were treated by paravertebral deep intramuscular injection. Of 28 cases treated with novocaine, 16 (57 per cent) obtained relief. Of 17 cases treated with normal salt solution, 9 (53 per cent) obtained relief. Of 17 cases treated by the needle alone, 10 (59 per cent) obtained relief. The percentage of permanent relief was somewhat higher in the novocaine series than in the others.

3. An analysis of these results is presented with regard to the substance injected, the area and depth of the injection, the clinical diagnosis, the functional element, the effect of previous treatment, the duration of complaints, the type of pain on injection and its relation to the original pain, the immediate effects of the injection and the alteration in the physical signs.

4. An evaluation of the injection method of treatment is offered, its rationale discussed and its uses and limitations defined.

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SCREENING FOR TUBERCULOSIS IN A CIVILIAN POPULATION BY FLUOROGRAPHY *

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The control of tuberculosis must be based on the same general principles that are applicable to the control of all communicable diseases. Since there is no effective means so far developed for immunizing the population against tuberculosis, the efforts to prevent its occurrence must rest largely on limiting the spread of the organism responsible for the cause of the disease. Since bovine tuberculosis has been so well controlled in this country the one remaining important source of tubercle bacilli is the persons who have tuberculosis. It therefore becomes of prime importance to detect as far as possible all the cases of tuberculosis in the community not only for the sake of finding them early when a good chance of recovery exists but also before they have had any opportunity to spread the infection to those about them.

The insidiousness of the onset of tuberculosis either through lack of symptoms at all or the presence of symptoms like those of a cold or other respiratory disease not regarded too seriously by the patient makes it very apparent that if the patient waits until he has really become ill enough to seek his physician's advice he will often have progressed well beyond the early stages of the disease. This, in part at least, has accounted for so many cases failing to be recognized before they have reached a far advanced stage when recovery is more difficult and when they have probably unwittingly been spreaders of infection for some time.

The examination of large groups of presumably well persons for the detection of tuberculosis has therefore come to be looked upon as sound practice since every early case discovered means savings to the individual, the family and the community in lessened hospital care and in less chance of infecting others.

Edwards [1] of New York has shown the usefulness of mass surveys of large groups in uncovering tuberculosis particularly when such surveys are conducted in groups that previous experience has shown have a greater prevalence of this disease than that of the rest of the community.

In searching for tuberculosis it is most important to find the pulmonary cases since they are most likely to be in a communicable state. Although the extra-pulmonary cases of tuberculosis may occasionally be infectious they are much less apt to be so and of course are much less in number than the pulmonary cases. On this basis then survey methods are designed to detect the pulmonary forms of tuberculosis.

* Read at the Boston meeting of the American College of Physicians, April 25, 1941.

Everyone is familiar with the use of the tuberculin-roentgen-ray survey technic in which a tuberculin test is used to indicate those who may at some time have been infected with the tubercle bacillus, and the roentgen-ray of the chest was applied to all those reactors to determine whether there might be actual disease present. This method of survey was first extensively used in Massachusetts in the now famous Chadwick Clinics for the discovery of tuberculosis in school children. Although this method has been successfully used for some time, it has been felt by many workers that if a more economical yet reasonably accurate method of roentgen-ray examination could be developed it would be a more practical survey method with less chance of error when applied directly to the whole group without previous tuberculin screening.

Accordingly many efforts have been directed toward producing a less expensive type of roentgen-ray examination, with varying degrees of success. Sensitized paper, the direct fluoroscopic examination, and more recently the photography of the fluorescent image on the fluoroscopic screen using small film of various sizes have been developed to meet the requirement of economy in surveys.

The authors have had the opportunity to use one of the fluorographic methods for the past two years in case finding surveys, the results of which have been very satisfactory.

The method used was that developed by Dr. Hollis E. Potter [2] in collaboration with the laboratories of the General Electric X-ray Corporation.

This fluorographic method employs a specially built lens in a camera screen unit capable of making a photograph of the fluorescent image on a 4×5 inch film. This size was arrived at after extensive study as being most desirable since it is large enough to be readily interpreted without enlargement and yet small enough to make a real saving in material cost, namely, about one-tenth the cost of the full size film.

The source of roentgen-ray for this type of work must be good. At least a 200 milliampere tube should be used and even more brilliant films can be taken if a rotating anode tube allowing the use of 400 milliamperes is used since this will allow a greater target-screen distance and a shorter exposure.

Careful checking as to the accuracy of this method by taking films of a large number of patients with both the regular film and the small size revealed an error of 2.6 per cent in failure to detect certain very small lesions. This work has been reported in detail elsewhere.[3] More recently Bridge [4] in a similar study reported less than 1 per cent error.

Since questionable lesions may be better visualized on a large film such patients may be called back for large films but in the experience of the authors this has not been necessary except in a relatively small number. For example, it was found necessary to call back only 51 persons for re-check on a large film in a consecutive series of 6,104 small films.

These small films can be made rapidly, better than one a minute, which is as rapidly as persons can be prepared for examination and handled conveniently through most clinics.

This method has been used now for over a year and a half in the outpatient department of the Herman Kiefer Hospital for the examination of contacts and those suspected of tuberculosis. Over 30,000 such examinations have been made and have proved very satisfactory in determining the presence or absence of pulmonary tuberculosis of an amount necessary to require hospitalization. For the careful work of determining the type of treatment and controlling the progress of the patient in the hospital the small films have not been used since here the utmost of detail is required, often stereoscopic studies, Bucky diaphragm films, or perhaps section roentgenography.

The follow-up of patients discharged from the hospital or sanatorium is also being done at the clinic with the fluorograph. The economy of this examination makes it possible to examine more frequently than was possible with the previously limited number of large films available.

Several groups other than the contacts and suspects examined in the tuberculosis clinic mentioned have been studied on the basis of surveying those whose situation might make them more likely to have tuberculosis than others. One of the first of these groups in which continuous roentgen-raying was started was made up of the women attending the pre-natal clinics of the Health Department. In order to make a short study of the merit of roentgen-raying all of the group as compared with tuberculin testing and roentgen-raying only the reactors, the first 1,425 women were all tuberculin tested and a fluorograph of 4 × 5 inch size made.[5] The tuberculin test was a single intradermal test using 1–1000 O.T., the so-called middle strength often used as a single dose tuberculin screen. Of these women 144 failed to return for a reading of the test and it is interesting to note that among these there were two active cases, one moderately advanced and one far advanced, found by roentgen-ray since these had all been rayed. Of those returning to have the test read 610, or 47.6 per cent, were positive. Among the positives were three active cases. Among the 671 negatives to the single dose were two active cases, later found to be positive to stronger dosage. This is a small number from which to draw conclusions and yet this study suggests the possibility of missed cases from failure to return for reading of the test and failure to respond to a single dose of tuberculin, all of which may be obviated by one visit for a fluorograph of the chest.

Since October 1939, 4,727 prospective mothers have been fluorographed and 29 active cases found, an incidence of 6.1 per 1000 examined. Of these cases five were active primary cases, eleven minimal pulmonary, eight moderately advanced, three far advanced and two pleurisy with effusion.

This is a useful survey since it affords a chance for prompt treatment for the expectant mother and also safeguards the expected child against early infection through knowledge of the mother's state at birth.

A smaller group of the population surveyed has been a group of women working under W.P.A. as housekeepers in poor families. This has been a comparatively healthy group—among 751 women only 4 cases, or 5.3 per 1000, were found. One was minimal pulmonary, two moderately advanced, and one far advanced.

A study of the City of Detroit each year for the prevalence of tuberculosis cases reported by census areas and tuberculosis mortality rates by these areas has been quite revealing in showing wide variation in the amount of tuberculosis apparently present in various parts of the city. For instance, in 1939 when planning where extensive roentgen-ray service might be provided in a population showing the most severe experience with tuberculosis one area with over 200,000 population had a mortality rate from tuberculosis of 126 per 100,000 per year in comparison with a nearby area of slightly greater population but living under much better conditions with less congestion where the mortality rate was only 19 per 100,000.

A second fluorographic unit therefore was placed in the midst of this high mortality area in the summer of 1940 for the purpose of getting as many people as possible to come in for examination. Although it has not been possible to do any extensive house to house visiting in this area to encourage people to be examined and only voluntary efforts have been relied on, 9,326 persons have come in for examination up to March 1 of this year. Of the 8,322 of these in which the results have been checked for previously reported cases and other duplications, 121 cases have been found, or 14.5 per 1000 examined, which is definitely more than the number found in other groups. This population was 94 per cent negro. Of the 121 cases found, 22 were active primary tuberculosis, 29 minimal pulmonary, 30 moderately advanced pulmonary, 25 far advanced, 3 miliary and 12 pleurisy with effusion.

A group of young persons selected for N.Y.A. service has recently been examined and though the group is small, 1,420, the results indicate that this age group of working young men and women have a significant amount of tuberculosis since 9 cases have been found, or 6.3 per 1000. Four of these were minimal, two moderately advanced and three far advanced.

The following table summarizes the results in each of these four groups surveyed so far:

TYPES OF CASES FOUND BY GROUPS

Group	Total Examined	Cases Found							
		Prim. Act.	Min.	Mod. Adv.	Far Adv.	Miliary	Pleur. with Eff.	Total Cases	Incidence per 1000
Brewster Project	8,322	22	29	30	25	3	12	121	14.5
Pre-Natal Mothers	4,727	5	11	8	3	0	2	29	6.1
Housekeepers	751	0	1	2	1	0	0	4	5.3
N. Y. A.	1,420	0	4	2	3	0	0	9	6.3
	15,220	27	45	42	32	3	14	163	10.7

Summary

The 4 × 5 inch fluorograph has proved useful and practical in tuberculosis case finding. Application to several different groups has demonstrated that there are significant numbers of persons with tuberculosis to be found.

From a comparison of this method with other methods of roentgen-ray examination it is believed: first, that while the full sized film is the most accurate method, still it is too expensive for survey use; second, the sensitized paper is good but is still too expensive (about one-half the cost of celluloid film) and in addition is bulky to handle and store; third, the fluoroscope is not nearly as accurate as film methods and there is no permanent record (the error in fluoroscopy according to Fellows [6] is 13 per cent when compared with large films); fourth, the miniature 35 mm. film, used most extensively by De Abreu [7] of Brazil and now being used by a number of persons in this country, it is believed sacrifices too much in accuracy in favor of economy. These very small films must be enlarged before they can be interpreted. Recently a stereoscopic technic for these very small films has been developed which improves them a great deal but still leaves much to be desired in detail.

Conclusions

The authors feel justified after this experience with the 4 × 5 inch fluorograph in concluding that:

1. It is a reasonably accurate method of making a roentgen-ray examination of the chest.
2. Applied directly to a group without previous tuberculin screening the fluorograph has definite advantages.
3. It lends itself well to group surveys.
4. Surveys of certain groups in the community are definitely profitable through the discovery of many previously unrecognized cases.
5. Wider application of fluorographic examinations will aid in the control of tuberculosis through better case finding.

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FAMILIAL ACHOLURIC JAUNDICE ASSOCIATED WITH BONE CHANGES *

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Familial acholuric jaundice, frequently called congenital hemolytic icterus, is a relatively uncommon disease. In a city of approximately one million inhabitants, Melbourne, Australia, there are at least three families known to be afflicted with this inherited blood dyscrasia.

The family here recorded is apparently in no way connected with any of the families previously reported from Australia and the patients present rather unusual bone and facial abnormalities.

In all, 10 individuals in three generations have been affected. Three case histories follow:

Case Reports

Case 1. Myra B., a female aged 14 years, was admitted to hospital in 1921 after attacks of jaundice which had recurred since early childhood. Her father and two paternal aunts had suffered from jaundice and enlargement of the spleen.

The patient had a red blood cell count of 3,800,000 per cubic millimeter, the leukocyte count was 8,000 per cubic millimeter and the stained film of the blood appeared normal. Tests of the fragility of red cells showed that hemolysis commenced at 0.525 per cent saline and was complete at 0.40 per cent saline. (In a normal control hemolysis began at 0.42 per cent sodium chloride.) The blood Wassermann test showed no fixation of complement. The urine contained bile pigment and the blood serum contained bilirubin in amounts larger than normal. The spleen, which extended well below the left costal margin, was removed at operation. There were dense adhesions between the spleen, the abdominal wall, and the stomach. Convalescence was uneventful and in the ensuing 15 years she had had no recurrence of jaundice. Her blood fragility is now within normal limits, hemolysis commencing at 0.45 per cent sodium chloride. Three years after the above operation Myra B. married and had seven pregnancies in 12 years.

Case 2. Merle A., eldest daughter of Myra B., was first seen in 1936 at the age of 11 years. She had been pale since birth and the anemia was so severe at the age of seven years that a transfusion of blood was administered. Since early infancy she had been subject to attacks of jaundice at intervals of four to five months. During these attacks of icterus the urine became very dark in color. There had been no abdominal pain. On examination, Merle A. was a bright looking child of above ordinary intelligence, small for her age but with a very large head and an extremely high forehead. The skull was shaped like a box but the sutures were not depressed. The eyes had a slant Mongolian appearance and the skin of the face was thick, greasy and of a muddy yellow-white color. The conjunctiva was slightly yellow when first seen. The trunk appeared short and the chest was large in the antero-posterior diameter. The abdomen was distended. The spleen was felt to one hand's breadth below the left costal margin and moved freely with respiration. No enlargement of the liver was detected. The child walked with a slight limp and roentgen-ray examination of the right hip revealed an early Legg-Perthes' deformity. Examination

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of the blood showed a red cell count of 4,260,000 per cu. mm., hemoglobin (Sahli) 60 per cent, color index 0.7 per cent; and a leukocyte count of 12,600 per cu. mm. The red cells in a film showed a definite microcytosis—there was some polychromatophilia and extreme anisocytosis and poikilocytosis. Reticulocytes were present to the extent of 24 per cent of all red cells. A fresh specimen of blood examined showed that the majority of the red cells were less bi-concave than usual and there was no rouleaux formation.

Fragility of red blood cells was abnormal; hemolysis commenced at 0.6 per cent sodium chloride and was complete at 0.45 per cent saline. In a normal control hemolysis began at 0.5 per cent saline. The blood serum was yellow; Fouchet test positive; quantitative van den Bergh 6 units; icteric index 26 (normal 4–6); blood cholesterol 210 mg. per 100 c.c. blood; serum calcium 13.5 mg. per 100 c.c.; plasma phosphorus 2.5 mg. per 100 c.c.; urine contained no bile pigments.

The roentgen-ray appearances of the skull will be described in detail later. In brief, the bones of the calvarium were enormously thickened with fine lines of denser bone radiating at right angles to the inner table. There was also an appearance similar to that seen in cerebral tumors described as hammered copper markings. The skull seemed very large in size for the age of the child. The facial bones and the skeleton in general showed no other abnormality, with the exception of the Perthes' disease in the right hip.

At operation under ether anesthesia the spleen, which weighed 30 ounces, was removed without difficulty through a left paramedian incision. There were numerous small stones in the cystic duct, and the gall-bladder, deeply buried in the liver, contained stones. These were not removed. Condition after operation was good but death inexplicably occurred 48 hours later. Postmortem examination revealed no obvious cause of death; the liver was small, soft, and fatty. The heart was enlarged and the cardiac muscle pale and friable. The bones of the skull were enormously thickened and the red diploë seemed to extend almost to the external surface of the bones. The red bone marrow of the femur extended throughout the length of the bone. There was no fatty marrow. The right femoral head was fragmented and flattened, a typical Legg-Perthes' osteochondritis.

On microscopic examination of the bones of the skull red bone marrow extended almost to the surface, and erosion of bone, new bone formation and fibrosis of marrow were seen in adjacent areas of the sections. The femoral bone marrow showed extreme erythropoietic activity. The spleen showed distention of pulp spaces, some fibrosis and endothelial activity.

Case 3. Robert A., male, aged 10 years, was seen in 1936. His skin had been yellow since birth and there had been recurrent attacks of intense jaundice. There were frequent attacks of colicky pain in the right upper abdomen. His mother stated that the child's head had always been large and box-shaped, and he had complained of frequent headaches.

On examination the boy had a Mongoloid face with definite exophthalmos. The skin was thick and muddy yellow in color. The spleen was palpable to the level of the umbilicus. The liver edge was palpable but there was no tenderness over the gall-bladder area. Examination of the blood showed red cells 4,000,000 per cu. mm., hemoglobin 60 per cent (Sahli) and white cells 15,600 per cu. mm. The film showed definite microcytosis. A few normoblasts were seen and 20 per cent of the red cells were reticulocytes. The red cells began to hemolyse at 0.6 per cent sodium chloride and hemolysis was complete at 0.45 per cent saline. The blood serum was yellow, the van den Bergh test showed a positive delayed direct reaction and the Fouchet test was positive. Roentgen-ray examination of the skull revealed thickening of the bones of the vault with vertical radiations like "hair growing from the inner table." The suture lines were obliterated (abnormally early for a child of ten). There was

no abnormality in the remainder of the skeleton. There was some chronic bronchitis and general cardiac enlargement.

A third child, Alan A., aged 8 years, brother of these two cases was also examined and he showed no abnormality in blood or skeleton.

Another brother had died at the age of seven years with acute nephritis—the mother stated that this child at the time of death was jaundiced and had a large spleen.

Twin girls had died at the age of three months from severe anemia and jaundice.

To summarize, the mother and two children suffered from acholuric jaundice, one child is normal and three children have died with what is presumed to be anemia, jaundice and splenomegaly.

Bone Changes

In descriptions of autopsies of acholuric jaundice there is frequent mention of red bone marrow replacing fatty bone marrow in the long bones. Even in adult cases the whole medullary cavity of the femur is occupied by erythropoietic tissue. Many observers have recorded extra-medullary hemopoiesis in acholuric jaundice. Dawson, 1931,[1] reported masses resembling bone marrow in the hilum of the kidney and in the costo-vertebral region in the thorax. Brannan, 1927,[2] recorded a similar case and also a patient with bone marrow in the broad ligament. Gleane, 1936,[3] reported large paravertebral masses of bone marrow 7 centimeters in length; these were not eroding the bone but apparently were extensions from the ribs or vertebrae into the loose connective tissues of the thorax.

Hyperplasia of red bone marrow as described above is usually confined within the marrow cavity. When, however, the hyperplasia begins in early infancy, before dense cortical bone limits extension of the marrow cavity, the shape of the bone may be determined to some extent by the bulk of the bone marrow. In chronic hemolytic jaundice, the call on bone marrow is continuous, the amount of marrow increases progressively and enlargement of the bone follows.

Even in early childhood the shape of the majority of the bones is already determined by a fairly dense cortex. But in the bones of the cranial vault the outer table does not form until later childhood. In the examination of 100 roentgen-ray films of children between the ages of one and twelve years the time of appearance of a definite outer table to the frontal and parietal bones was noted (personal observation). The actual year of appearance varies but it is rare for the outer table to be seen as a definite layer of compact bone before the age of six years. The bones of the cranial vault develop in membrane and the development of bone and bone marrow goes on side by side. Normally the growth of bone exceeds that of marrow until finally the marrow is confined to the diploë. A dense cortex forms on the external surface and thus arises an outer table similar to the inner table

which has appeared earlier in infancy. The progressive growth of bone marrow in the membranous bones of the cranial vault in acholuric jaundice leads to an enormous increase in the thickness of the diploë—furthermore, the diploë extends to the outer surface of the bone and the bony trabeculae of the diploë appear as relatively regular lines of bone formation arranged at right angles to the surface of the inner table of the bone. This radial ar-

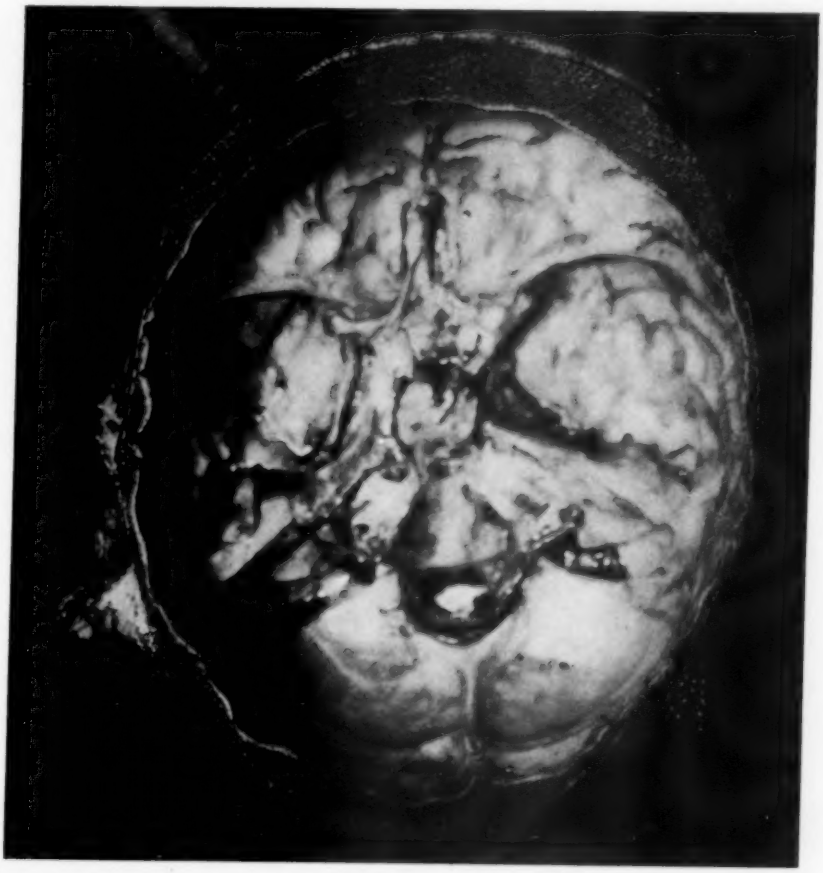

FIG. 1. Base of skull of M. A., showing enormous thickness of frontal and occipital bones.

rangement of bony trabeculae follows the deposition of bone by the mesenchymal cells of the membrane which is giving rise to the parietal and frontal bones. Hyperplastic red bone marrow largely replaces the osteoblastic tissues and the greater proportion of the thickness of the skull consists of masses of marrow separated by fine strands of bone.

Ground sections of the parietal bone show well the contrast between the deeper layers of the diploë and the newly formed superficial bone, and roentgen-ray photographs of these sections of bone show well the radial ap-

pearance of the superficial layers of bone. During life roentgen-ray films of the skull show a similar appearance which has been well described by Sear, 1928,[12] as like "hairs growing from the inner table."

Microscopically the bone of these vertical trabeculae shows irregular laminations and irregular ossification in the fibrous tissues. Active erythropoietic marrow tissue is everywhere in close contact with the bony trabeculae.

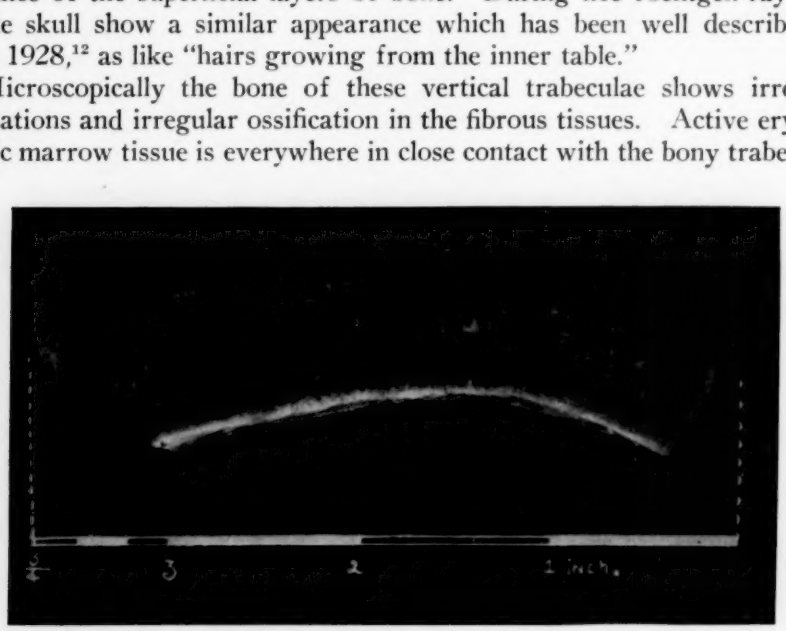

FIG. 2. Ground section of frontal bone of M. A., showing dense internal bone and porous bone throughout the remainder of the thickness.

There is a complete absence of any fat cells in the bone. In some areas the marrow shows degenerative changes and is partly replaced by dense scar tissue.

The evidence points to two distinct processes going on side by side in the bone. On the one hand there is active hyperplasia of bone marrow and formation of new bone; on the other there is an exhaustion of the overstimulated marrow and replacement of the degenerating cells by fibrous tissue.

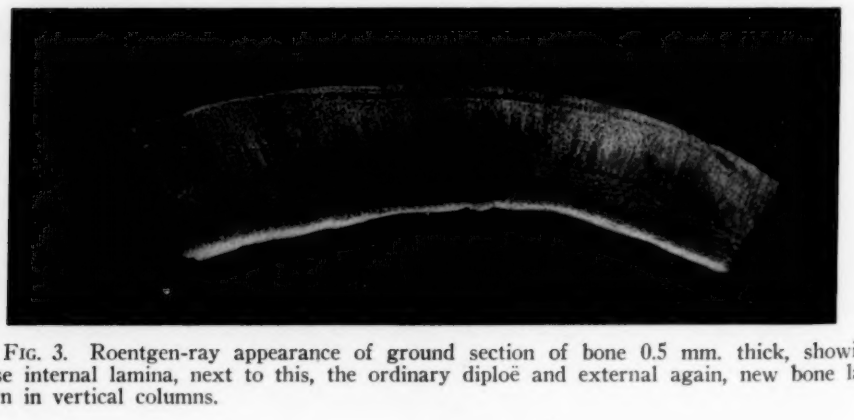

FIG. 3. Roentgen-ray appearance of ground section of bone 0.5 mm. thick, showing dense internal lamina, next to this, the ordinary diploë and external again, new bone laid down in vertical columns.

These changes have been described in some detail in the above case of acholuric jaundice. Exactly similar appearances are seen in Cooley's erythroblastic Mediterranean anemia (Mandeville, 1930[4]) and in sickle cell anemia of the negroid races (Grinnan, 1935,[5] Le Wald, 1932[6]). In these three conditions there is an extreme hyperplasia of bone marrow beginning in early childhood and resulting in the formation of red cells which are abnormal in type. These cells are destroyed more rapidly than normal red

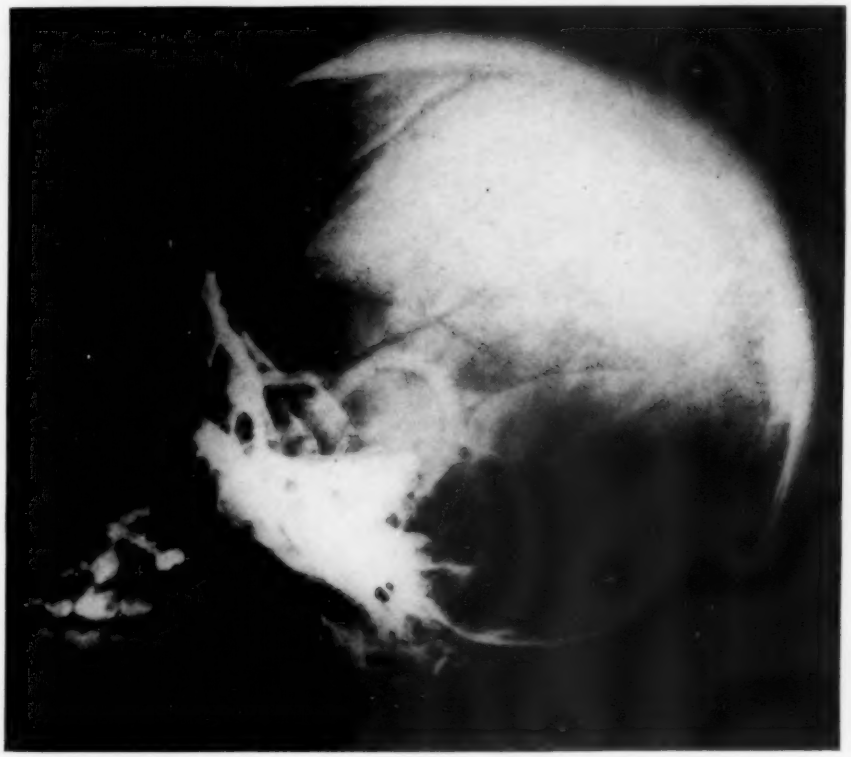

FIG. 4. Roentgen-ray of skull of M. A., showing thickened bones of skull-cap with vertical radiating lines ("hair growing through the outer table").

blood cells and thus there is a constant stimulus to marrow activity shown by the extreme reticulocytosis common to these three diseases (Whipple, Reeves and Cobb, 1928[7]).

Many other anemias are associated with active erythropoiesis but very few anemias arise so early in life. All three of the blood dyscrasias discussed (acholuric jaundice, sickle cell anemia, and erythroblastic anemia) may arise in utero or in early infancy (Cooley, 1928[8]). The stimulus to bone marrow begins before the outer tables of the membranous bones of the skull form. The result is an appearance characteristic of these three diseases.

This vertical striation is in some respects merely an exaggeration of a condition frequently seen in roentgen-ray films of the skull in childhood. It may be that anemias other than the congenital blood dyscrasias produce a mild grade of bone change, for the appearance of vertical striation is seen in the bones of the skull of apparently normal children.

Williams, 1929,[9] has reported similar changes in ancient skulls found in tombs in Peru, New Mexico and Arizona. Was familial acholuric jaundice,

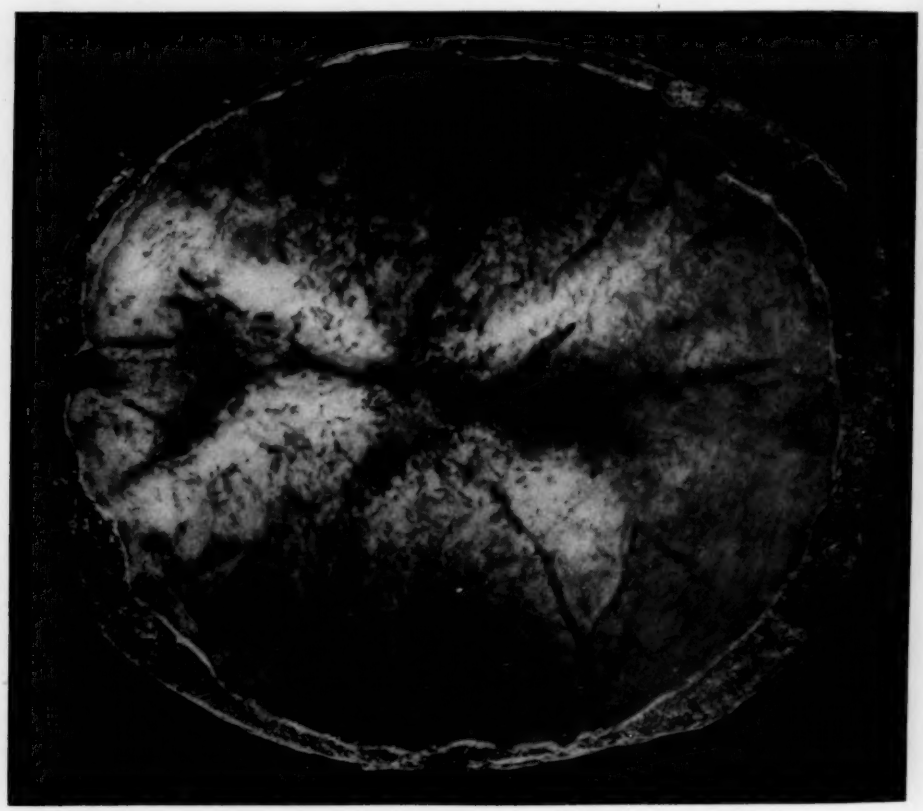

FIG. 5. Skull-cap of M.A., showing thickened bones of vault.

sickle cell anemia or erythroblastic anemia common in the families of the original inhabitants of central America, or is there some other explanation of these thickened skulls?

The relative rarity of bone changes in acholuric jaundice is remarkable in view of the large numbers of cases recorded.

Gännslen, 1936,[10] mentions changes in the bones and many of the American workers record the thick skulls described in this paper (Friedman, 1928[11]). Sear, Wade, and Steigrad[12] reported one case in Sydney exactly similar to the family recorded in this paper. No connection can be traced

between the Sydney and Melbourne families. Bone changes have not been found in the Hazel family reviewed by Cowen.[19]

On the contrary these bone changes are relatively common in sickle cell anemia (Feingold and Case, 1933,[13] and Rose, 1929[14]), and in erythroblastic anemia (Vogt and Diamond, 1929[15]). Although the majority of cases of

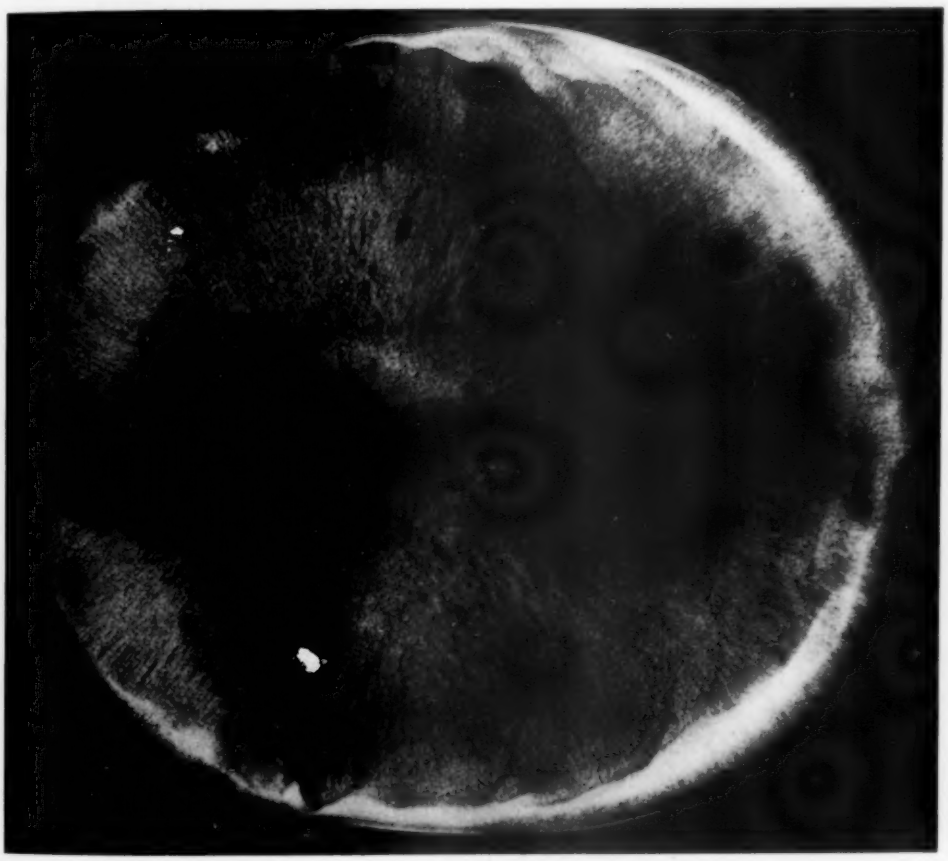

FIG. 6. Roentgen-ray of skull-cap of M.A., showing radiating lines of new bone formation.

acholuric jaundice are chronic in type, the stimulation of the bone marrow is more severe in the other two anemias and bone changes would be expected more frequently.

An alternative explanation is that the bone changes are an associated inherited anomaly. Some families and some races may transmit skeletal defects which render the bones of the skull more susceptible to the effects of severe anemia.

Similarities between Some of the Anemias

In hyperchromic macrocytic anemia the bone marrow discharges macrocytes owing to absence of the hemopoietic principle. These macrocytes are destroyed more easily than normal red cells resulting in an elevation of the blood bilirubin. The clinical picture of the lemon yellow skin of pernicious anemia is well known. Some patients with macrocytic anemia of the Addisonian type show a large amount of hemolysis. Reticulocytes are present in the blood stream to the extent of 5 per cent of the red cells, and the spleen may be greatly enlarged. In sickle cell anemia, described by Herrick and occurring as a familial disease in members of the negroid races, there is a defect in the structure of the red cells, and although the erythrocytes appear normal in the circulating blood, they assume a meniscoid or sickle shape some time after removal from the body. Meniscocyte formation is accelerated by exposure to carbon dioxide. The red cells are abnormal in other respects and are destroyed in large numbers in the enlarged spleen. A high blood reticulocyte count is usual and the bilirubin in the blood is markedly increased. In the erythroblastic anemia described by Cooley, 1927,[16] in people originally coming from the countries bordering on the Mediterranean Sea there is an abnormality of red cell formation resulting in the escape of enormous numbers of nucleated red blood cells from the red bone marrow. These erythroblasts are destroyed rapidly resulting in reticulocytosis, splenomegaly and a high percentage of bilirubin in the blood serum (Baty, Blackfan, and Diamond, 1932[17]).

In familial acholuric jaundice the red cells discharged from the bone marrow are less resistant to hypotonic sodium chloride solutions than normal cells. The red cell is also thicker than normal and the name spherocyte has been given to this abnormal cell. These cells are destroyed in large numbers resulting in splenomegaly, reticulocytosis and bilirubinemia.

Thus in all these anemias abnormal red cells are destroyed by the normal mechanism. In macrocytic hyperchromic anemia of the Addisonian type the abnormality of the red cells can be corrected by the administration of the hematinic principle contained in liver. The other three dyscrasias at present are not susceptible to treatment by replacement therapy.

Acholuric jaundice is relieved by splenectomy but in the majority of patients the fragility of the red blood cells is unaffected. Sickle cell anemia and erythroblastic anemias are as yet not influenced by medical or surgical treatment. Chronic ulcers in the leg are common in patients with acholuric jaundice; these ulcers heal after splenectomy is performed. Similar ulcers occur in Cooley's anemia and sickle cell anemia (Graham, 1924[18]).

Cooley's erythroblastic anemia and familial acholuric jaundice are both associated with a peculiar change in facial appearance. This is described by Cooley as Mongoloid and includes prominent eyes with puffy eyelids—high malar eminences and nose short with depressed bridge. The skin is a muddy

yellow color and feels thicker than normal. The head is large and irregularly shaped with prominent frontal and parietal bones. The Mongoloid appearance of the face is commoner in Cooley's erythroblastic anemia.

The members of the family recorded in this paper show a similar facies associated with bone changes in the vault of the skull but with normal facial bones.

These changes in the soft tissues cannot be related directly to either the blood abnormality or the changes in the skull bones. The Mongoloid face can be described only as an associated anomaly inherited with the blood dyscrasia. This does not explain the frequency of the Mongoloid face in Cooley's anemia, the rarity in acholuric jaundice and its absence from the records of patients with sickle cell anemia.

In summary:

(1) A new family is recorded of familial acholuric jaundice or hemolytic splenomegaly of Chauffard-Minkowski type.

(2) This family shows the Mongoloid facies described by Cooley in erythroblastic anemia and also the changes in the bones of the skull reported in sickle cell anemia and erythroblastic anemia.

(3) A description of the bone changes is given and an explanation of the localization to the skull is attempted.

(4) The relationships of the three related red cell dyscrasias—acholuric jaundice, sickle cell anemia and erythroblastic anemias—are discussed.

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NEUROLOGICAL, MEDICAL AND BIOCHEMICAL SIGNS AND SYMPTOMS INDICATING CHRONIC INDUSTRIAL CARBON DISULPHIDE ABSORPTION *

By F. H. Lewey, M.D., *Philadelphia, Pennsylvania*

According to the statistics of the Textile Economics Bureau, 78,000,000 pounds of carbon disulphide (CS_2) were employed in 1937 in the 19 viscose rayon plants operating in the United States of America. Thousands of workers were thus exposed to the potential danger of absorbing CS_2 fumes and falling victim to intoxication. Despite this fact five short case histories published before 1905 (Bard,[1] Peterson,[2] Heath,[3] Jump and Cruice,[4] Francine,[5] and one report of recent years (Gordy and Trumper [6])) constitute all that American medicine has contributed to this subject.

Credit should be given to Dr. Alice Hamilton for 15 years of relentless and eventually successful crusade against the danger of CS_2 intoxication in viscose rayon plants. Dr. Hamilton had listed this risk as early as 1925.[7] In 1937 [8] she raised again her warning voice to point out that "the lack of interest in the pathological signs and symptoms accompanying and following industrial CS_2 poisoning was in inverse proportion to its medical and sociological importance in this country which is the second largest producer of rayon in the world." Finally, in 1938, Dr. Hamilton found a propitious constellation in the Commonwealth of Pennsylvania enabling her to induce the Department of Labor and Industry to conduct—with the energetic assistance of Miss Lillian Erskine, then Consulting Expert of the Department—a "Survey of Carbon Disulphide and Hydrogen Sulphide Hazards in the Viscose Rayon Industry." [9] †

Requested to act as Consultant to the State in this investigation I had the good fortune to secure the coöperation of the various departments of the University of Pennsylvania Medical School. Thus, 120 workers were examined by a neurologist, psychiatrist, ophthalmologist, otologist, internist and hematologist. Finally, a number of biochemical studies were made (Hamilton and Lewey [10]).

The scientific gains of these examinations are reported in this and in the papers of Dr. F. J. Braceland [11a] and Dr. B. J. Alpers and myself,[11b] as well as in a previous paper of Dr. R. McDonald.[12] The beneficial practical result of the coöperative investigation was that the rayon industry in this State became deeply concerned with the problem. It availed itself of experts in the

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From the Neurosurgical Department in the Hospital of the University of Pennsylvania.

This investigation was conducted under the auspices of the Department of Labor and Industry in the Commonwealth of Pennsylvania.

† See here for the complete literature of the subject.

field of Industrial Hygiene and is going to reduce the inherent risk of the manufacturing process to a minimum with the help of adequate control of ventilation and automatic machinery.

This paper does not deal with acute CS_2 intoxications but with the consequence of exposure to CS_2 fumes over a long period of life. We prefer to use the term "CS_2 absorption" in reporting the findings in these individuals because all of them, with three exceptions, were actually working at the time of the examination and did not consider themselves ill, although they admitted various complaints when specifically questioned.

Grouping of Patients and Histories

For the sake of expediency, each of the 120 viscose rayon workers examined was graded according to the severity of signs and symptoms in a conference of six medical specialists from the University of Pennsylvania Hospital coöperating in this investigation. It is obvious that such a grading will always be more or less arbitrary, although certain numerical principles were applied as a basis for judgment. The general appearance and condition of the individual, however, could not be neglected. As a whole, it was surprising to notice in how few instances there was any dissension among the six specialists concerning the severity of a case.

In the following, the history of representatives of two of the four groups, namely: mild (I), moderately severe (II), severe (III), and very severe (IV) cases, is given as an example.

Group I, comprising almost 40 per cent of the examined, represents the largest group.

L. C., aged 42, of English descent, had worked for over 13 years in the spinning department of a viscose rayon plant. He was married, had one child, and lived in moderate circumstances. He had never been severely ill, did not use any medicine, and had not spent any money for personal medicine during the preceding few years. About six or seven years previously, i.e., at the age of 35 or 36, he began to lose both libido and sexual power. Later he noticed shortness of breath and nausea before meals although his appetite remained fair. During the preceding two years he had begun to suffer from frontal and occipital headaches and from dizziness when stooping over. Sleep became poor. His hands got numb while asleep, and he had to rub his arms when he awakened. At times he had the sensation of pins and needles in his arms. His calves sometimes ached so badly that he had to prop up his feet to get relief.

The following pathological signs were observed:

P. E.: Slurring of the ventricular complex in electrocardiogram; liver slightly enlarged; bleeding of gums; and ecchymoses.

N. E.: Pupillary reflexes to light slightly decreased (7.2 per cent)*; corneal reflexes markedly decreased (0.68 mg./mm.^{2})†; marked dip in the audiometer curve at 4,096 frequencies; slight nystagmus on right and left gazes; Troemner sign of the

* The pupillary reflex was measured with the Hess-Zeiss pupilloscope. See Adler, F. H.: Clinical physiology of the eye, 1933, The MacMillan Company, New York, p. 63.

† The corneal reflex was measured with graded jets of air. For normal values see table 3.

right hand; hyperactive patellar and Achilles reflexes. When the arms were extended and the eyes closed, the left arm sank. Pastpointing downward with the left arm; tenderness to pressure over both radial nerves; mild electrical underexcitability of the ulnar nerves (7.3$\sqrt{\mu}$C).*

Diagnosis: Mild polyneuropathy, possibly with involvement of the central nervous system.

Going over this history, one might be impressed by the variety and comparative gravity of symptoms. However, the man himself was so little impressed by them that he did not even consider consulting his physician. A hardy individual, he was not concerned by minor inconveniences which, in his opinion, were too slight to worry about.

There were only three pathological signs which occurred frequently in this group. About one-third of the 47 persons in Group I showed a decrease of the pupillary and corneal reflexes, and about one-half showed a pathological electrical irritability in the peripheral nerve-muscle apparatus. Nystagmus was observed in 17 per cent of them; the remainder of the signs were present in less than 10 per cent (table 3).

Not one of these signs alone gives conclusive evidence of CS_2 absorption, but their combination should always arouse the curiosity of the family doctor, or the consultant, as to the occupation of his patient.

Group II comprises almost 30 per cent of all examined.

The main difference between Groups I and II lies in the increasing frequency with which the various neurological signs appear in Group II. Indeed, some of them, such as nystagmus and tremor, reach their greatest incidence in Group II, while in most of the columns the percentage of pathological signs rises considerably (table 3). As a matter of fact, the gap in the frequency of pathological signs between Groups I and II is greater in all columns than between II and III, and often greater than between II and IV. No increase in frequency from Group I to Group II is visible in the charts recording the electrical over- or underexcitability of the peripheral nerves. However, the *frequency* with which specific pathological signs appear in each of the four groups is only one standard of severity. We shall see later that, at least in some syndromes, the *severity* of the phenomena themselves plays a preëminent rôle in the final grading of the individual.

Group III consists of 22 workers, or 18.3 per cent of all examined.

P. D., aged 54, was married and the father of six living children. He had worked in the churn room of a viscose rayon plant for almost 19 years. He had suffered from headaches for many years but was not so greatly troubled at the time. He was easily fatigued, restless and sleepless; stated that he jerked in his sleep, and complained of vertigo. He was constipated and took a laxative twice a week; his appetite was poor and he was often nauseated. His arms and legs were numb. At times the right arm felt as though it were stiff and paralyzed. His legs felt heavy and he had great difficulty in ascending stairs. He trembled upon the slightest exertion or excitement.

* Microcoulomb is the product of voltage times microfarad or time in milliseconds. For technical reasons the actual figures are given as the square root of microcoulombs ($\sqrt{\mu}$C). The normal values for the various muscle groups are given in table 4.

The following *physical* and *laboratory* signs were found: Aorta tortuous; blood pressure 150 mm. Hg systolic and 100 mm. diastolic; blood picture normal; serum cholesterol 266 mg. per cent; urine normal; CS_2 excretion in urine 25–50 γ per cent, or 0.3–0.6 mg. in 24 hours.

Neurological examination: Slight pallor of optic discs; marked decrease of pupillary reflexes to light (right, 19.4 per cent; left, 24.6 per cent); slight decrease of corneal reflexes (0.43 and 0.5 mg./mm.^{2}); short choreic movements of the extremities, and continual twiching movements in the muscles of the arms and legs were present. A strongly positive Noica sign was elicited in both arms. The left arm did not swing in walking. A positive reaction of convergence was observed in the left arm in testing postural reflexes. Knee jerks were hypoactive, Achilles reflexes absent bilaterally. There was decrease of pain sensitivity in the left arm and leg, and tenderness to pressure on left radial and ulnar nerves. The electrical irritability of the flexor muscles of the fingers was mildly decreased (6.2$\sqrt{\mu}$C), of the peroneal muscles moderately decreased (6.4$\sqrt{\mu}$C). There was a reversal of the polar formula in the former.

Diagnosis: Thalamic syndrome without involvement of the pyramidal tracts, and mild polyneuropathy.

A syndrome such as cited above might well be expected following apoplexy, but the most intensive inquiry failed to show any trace of such. We are, therefore, bound to accept the assumption that a purely degenerative process is present here.

In general, Group III is marked by an increase of pyramidal and extrapyramidal signs, i.e., signs of central origin.

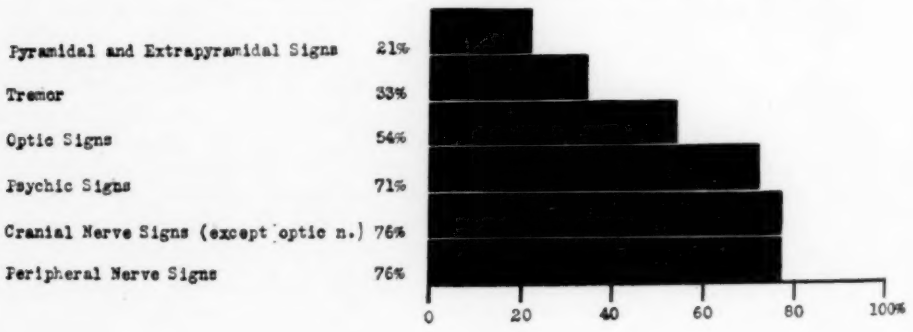
The small Group IV is composed of 10 individuals, or 8.3 per cent of those examined.

Neurological Signs and Symptoms

The frequency with which pathological signs and symptoms were observed in the 120 persons included in this investigation is illustrated by the following chart (table 1):

Table I

Frequency of Signs of Nervous and Psychic Disturbances, Expressed in Percentages of Examination of 120 Viscose Rayon Workers



The graph demonstrates that the peripheral and cranial nerves (excluding the optic nerve), and the hemispheres (as evidenced by mental symptoms), were most commonly affected in CS_2 absorption.

Disease of the nerves of the extremities is the commonest and most characteristic sign of CS_2 absorption and intoxication; 76 per cent of the 120 workers showed signs of mono- or polyneuropathy.

The sensation of pins and needles, of crawling ants, a strange itching soreness (often developing from contact with rough or cold objects), and "dead" fingers (as the result of inconvenient positions of the arm) are among the earliest complaints. Arms and legs show a tendency to "fall asleep." Constant or paroxysmal pains in the muscles, especially of the calves, and in the distribution of one or several peripheral nerves are common complaints. Shooting pains in the legs often reach an intolerable intensity during the night.

Objective signs of sensory disturbance, such as tenderness of the peripheral nerves to pressure, and areas of hyperpathia have been observed in 21.7 per cent of our group; less frequently decrease of sensitivity to touch and pinprick has been noted. Ataxia and a pseudo-Romberg sign were found in 26.7 per cent.

Disease of the motor portion of the peripheral nerves, as signified by electrical over- and underexcitability, was found in 56.7 per cent. In 9.2 per cent overexcitability was seen. The mean values for the four groups are given in table 4. It may not be amiss to point out here that actual motor weakness was not found in our group of workers and that galvanic overexcitability and reaction of degeneration were seen only in a few persons. Determination of the strength-duration curve is the only way of detecting the early stages of neuropathy observed in our group.

Decrease of tendon reflexes and presence of hyperpathic areas as well as decreased sensitivity and tenderness of nerve trunks, appear to be related statistically to disease of the peripheral nerves, not of the central nervous system (table 2).

Cranial nerves: Facial weakness is a rare finding in CS_2 workers. It was observed by us in only four instances. Three times it was of peripheral and once of central origin. Deviation of the tongue was slightly more frequent (10.8 per cent). Decrease of the corneal reflexes is considered one of the earliest objective signs of CS_2 absorption, whereas decrease of pupillary reflexes to light was present in about 50 per cent of our workers when examined with the Hess pupilloscope. The mean values for the four groups of severity are given in table 3. Nystagmus was one of the most frequent signs observed (77 per cent). A dip in the audiometer curve was also commonly found; workers examined showed no signs of nerve deafness but a lacuna in the hearing curve at the frequency of 4096 double vibrations (Dr. O. V. Batson [9]). This hearing deficit is located above the frequencies used in speech. The isolated deficit may be caused by exposure to CS_2 or an-

other toxin affecting the cochlear nerve, such as tobacco and alcohol (Carroll and Ireland[13]), but is also present in a large number of persons for unknown reasons. The difficulties in hearing complained of by many of our workers were found not to be caused by a lesion in the hearing organ, but by the inability of the individuals to fix their attention on conversation.

The psychic symptoms which have been described in detail by F. J. Braceland[11a] are of the order of toxic psychoses. Severe insomnia and constant bad, fearful dreams are the initial symptoms, followed by rather severe memory defects and, finally, by extreme irritability and uncontrollable anger with rapid mood changes. Acute true psychoses, usually of the maniacal type, were seen in some instances though outside of the group of workers here described. Reversible interference with sexual functions in individuals below the age of 45 was reported by about 75 per cent of those examined.

The ocular signs of CS_2 absorption among viscose rayon employees have been discussed in detail by one of our coworkers, Dr. Robb McDonald.[12] It is sufficient to mention here that contraction of the peripheral visual fields, blurring of the optic discs, and enlargement of blind spots up to four times their normal size, have all been observed, the last in almost one-fourth of all those examined. Two persons gave a history suggestive of having had a central scotoma at some previous time, and one was found to have poor central color vision. Arteriolar-sclerosis was found in a number of individuals far below the usual age for its occurrence. However, the majority of ocular complaints were due to lack of proper glasses.

Some signs of involvement of the pyramidal or extrapyramidal system were present in 27.5 per cent of our material; 21.7 per cent, or about every sixth man, showed the more or less characteristic picture of Parkinsonism. Quarelli,[14] in Italy, who first described this syndrome in CS_2 intoxication, saw it in 30 per cent of the viscose rayon workers of Torino. Many of his patients, according to a report of Audo-Gianotti,[15] showed tremor as the only sign of Parkinsonism; but in many cases the tremor was a static one, disappearing in repose and increasing on voluntary movements. In other words, not every tremor in CS_2 absorption is a Parkinson tremor. We based our diagnosis essentially on the appearance of the individual, his behavior, rigidity, the absence of arm-swinging in walking, positional and postural reflexes, and the Noica test. Parkinsonism in CS_2 may or may not be combined with polyneuropathy. In some instances, signs indicating a lesion of the basal ganglia were found combined with those pointing to involvement of the optic thalamus. We saw three persons with a typical thalamic syndrome.

Poor exercise tolerance, palpitation, shortness of breath, precordial and substernal pain were common complaints in this group of workers and were suggestive of some cardiac derangement (Dr. S. Bellet). Objective signs of cardiovascular disease were seen in about one-third of all examined, though they were of minor nature in some instances. Bradycardia ranging from 50 to 60 pulse beats per minute was frequently observed. Electro-

cardiographic changes were found in every eighth of our viscose rayon workers. They consisted of slurring of the ventricular complex, depression of the S–T interval and inversion of the T-wave. Arteriosclerosis of peripheral and retinal blood vessels with or without associated arterial hypertension or angina pectoris in young persons was more frequently observed in this group than in the average of the entire population. Our human material is not great enough to indicate in itself a definite causal relationship between the cardiovascular changes and the CS_2 absorption. It may be of significance in this connection that dogs during experimental chronic CS_2 intoxication developed retinal spasms and a negative T-wave in the electrocardiogram and showed marked arteriofibrosis of the cortical blood vessels.[23]

Biochemical Examinations: The spinal fluid has been examined in a number of persons with CS_2 intoxication, not included in this study, and has always been found normal.

Determination of CS_2 in blood and urine of viscose rayon workers has been made in two factories by J. H. Frank, with his xanthogenate method, about 30 to 60 minutes after the workers had left the plant. In the one plant, of a group of 19 workers only one (5 per cent) did not show CS_2 in his blood; the others, churn room and spinning room workers, had a mean of 409 ± 248 * γ CS_2 with a range from 129 to 1219 γ. The urine values of CS_2 in this group were 27 ± 6.3 γ, with a range between 20 and 50 γ. In the other factory, of a group of nine spinning room workers, two were negative in the blood test, one showed traces and six a mean of 15 ± 7.5 γ one hour after leaving the plant. The urine in the same group at the same time was negative in five, showed traces in three, and 6 γ in one man. Our systematic experimental investigations, in addition to the clinical data, suggest that CS_2 is eliminated from the body within about four hours from the blood and probably within a day from the urine. This fact limits the possibility of proving the nature of intoxication.

The porphyrine excretion in the 24 hour urine specimens of eight workers exceeded the normal figures (0.03 to 0.05 mg.) in only one instance (0.07 mg.) (Dr. J. H. Austin).

Serum cholesterol. In a random sample of 100 normal individuals the mean of the total serum cholesterols was 178.28 mg. per cent with a standard error of 1.3 and a standard deviation of 13.11 mg. per cent, of which about 60 per cent were esters. The mean of the total cholesterol values was 34 per cent higher in the 54 CS_2 workers than in the normal workers, simultaneously with a fall of the percentage of the cholesterol esters (238 mg. per cent total cholesterol with a standard error of 6.1 and a standard deviation of 44 mg. per cent, of which 44 mg. per cent were esters (Dr. J. G. Reinhold)). The high serum cholesterol value was found not to be associated statistically with retinal or peripheral arteriosclerosis, but seems to represent an independent disturbance of metabolism, possibly a toxic disorder of the liver function.

* The second figure means in this paragraph standard deviation.

Hematological studies (Dr. A. J. Creskoff) revealed rather normal conditions except for a slight increase in the monocyte percentage. The monocytes also showed certain indications of toxicity (basophilia, toxic granulations).

Pointing to dysfunction of the liver is furthermore the fact that in 20.8 per cent of all persons examined, varying degrees of sore, red, smooth, or atrophic tongues were recorded, while 8.3 per cent suffered from ecchymoses and frequently bleeding gums and noses. These observations, together with polyneuropathy, are suggestive of a vitamin B deficiency.

The average thiamine excretion in 24 hour specimens of urine from five normal individuals was found to be 516 γ with a standard error of 25.8 and a standard deviation of 141 γ in 30 determinations performed by Jolliffe, Goodhart, Gennis and Cline.[16] Dr. Leon Jonas examined the 24 hour specimens of eight spinning room workers.* One of them had a normal excretion of 405 γ; the other seven had values ranging from 54 to 197 γ.

It may be mentioned in passing that the person with the lowest thiamine output (54 γ) had the highest CS_2 content in his blood and urine (1 mg. and 50 γ respectively), and had, in addition, a cholesterol level of 328 mg. per cent. He was a member of Group IV, which contained the most severely affected persons.

Considering the rôle of the liver in vitamin B deficiency,[17] the increase of total cholesterol and the decrease of its esters in our workers (a phenomenon usually observed in severe liver damage), one might wonder whether CS_2, like carbon tetrachloride, does not act primarily upon the liver, depleting it of its vitamin stock and leading in this way secondarily to polyneuropathy. If this were so, a high-fat diet should have the same detrimental effect on the course of experimental CS_2 intoxication that it has in carbon tetrachloride poisoning. Our experiments on dogs suggest that this is the case.

Conclusions

There is no one symptom or sign characteristic of CS_2 absorption or intoxication, but the syndrome as a whole is fairly typical. Psychic symptoms such as sleeplessness and bad dreams followed by fatigue, listlessness and loss of initiative are usually the first and most consistent warning signs. They are accompanied very soon by disturbance of electrical excitability in some extremity muscles, and by decrease of the pupillary and corneal reflexes. Tenderness of nerve trunks to pressure, hyperpathic skin areas, paresthesias, and pain are common in CS_2 absorption, as are nystagmus and an isolated hearing loss at 4096 frequencies. Retrobulbar neuropathy, pyramidal signs and Parkinsonism may be present. The total serum cholesterol is often markedly increased, and the percentage of the esters simultaneously decreased. The thiamine excretion shows a tendency to low values. The spinal fluid is normal.

* Thiochrome for the thiamine determinations was furnished through the courtesy of Merck and Company, Rahway, New Jersey.

The presence of this syndrome should always arouse the suspicion of exposure to CS_2; but unless exposure can be established by factual testimony no direct proof can be evidenced by medical or chemical tests, since CS_2 disappears from blood and urine within a short time after the end of exposure.

Statistical Data and Their Evaluation

The majority of signs of disease here mentioned were discovered years ago without the aid of modern apparatus. There is no doubt that a piece of cotton wool and a pin are all that are necessary to detect motor weakness, sensory loss, decrease of corneal and pupillary reflexes, provided that the disturbance is massive enough to be seen with the naked eye. However, CS_2 intoxication is a good example of the experience that reliance on the "established" qualitative methods has led to erroneous statements such as that of the frequent occurrence of poor vision and hearing and, on the other hand, the overlooking of early stages of peripheral neuropathy and of the beginning decrease of corneal and pupillary reflexes. We like to stress the point that to our knowledge there is no way of early detection of this and many other neural diseases except by the application of the most sensitive apparatus giving numerical and reproducible results. The time has passed when the physician could complacently wait until his patients' symptoms and signs had reached the point where diagnosis could not possibly be missed. The recovery period from CS_2 poisoning is closely related to the hours of exposure. No instrument should be considered too complicated if with its help the time of absenteeism could be shortened. We have learned, finally, that in dealing with a great number of persons suffering from the same disease, and in integrating and combining their symptoms and signs, figures cannot always be taken at their face value but have to be examined for their significance. It should be understood that statistics is not a method of twisting the facts but of testing the validity of their interpretation.

We have mentioned that certain combinations of clinical signs and symptoms were found more frequently than others. It remains to demonstrate how far such an association could be considered as significant, i.e., probably not due to chance. Application of the chi square test shows a significant association only between the signs listed in table 2, A 1–5. The first computation indicates that CS_2 acts on the optic nerve, despite its central nature, in the same way as it does on peripheral nerves; the second shows that the vascular changes in the retina are probably not the result of a local process but part of a systemic vascular disease which finds its expression in arterial hypertension and electrocardiographic changes in younger people. Furthermore, decrease of pupillary and corneal reflexes is closely associated while their occurrence is not related to any other neural sign including abnormal electrical irritability of the peripheral nerves. In other words, there is no statistical evidence that the lesion responsible for the decrease of these two reflexes is situated in their afferent or efferent cranial nerves.

Finally, it is interesting to see that the occurrence of pyramidal and extrapyramidal signs is statistically not associated with disease of the peripheral nerves, i.e., is possibly due to a different mechanism.

It has been mentioned above that all cases were graded arbitrarily according to their severity by consensus of the six coöperating specialists. What significance can be attributed to this vote?

TABLE II

Significant Association between (*A*) Pathological Signs and between (*B*) Severity of Disease and Pathological Signs.

A.	1. Retrobulbar neuritis vs. peripheral neuropathy (incl. electr. irritability, contraction of visual fields, enlargement of blind spots);	P* = < 0.001
	2. Retinal vascular disease vs. peripheral vascular disease;	P = 0.05
	3. Decreased pupillary vs. corneal reflexes;	P = 0.05
	4. Pyramidal vs. extrapyramidal signs;	P = 0.0001
	5. Decreased electrical irritability vs. decreased tendon reflexes and sensitivity as well as presence of hyperpathic areas.	P = 0.01
B.	1. Severity of disease vs. disturbances of peripheral nerves (decrease of sensitivity, tenderness of nerve trunks, areas of hyperpathia);	P = 0.01
	2. Severity of disease vs. electrical irritability of nerve-muscle apparatus;	P = 0.034
	3. Severity of disease vs. psychic symptoms.	P = 0.05

* P indicates the probability that an association of the given amount or greater would occur in any random sample of a certain size taken from a universe in which there was no association between the given factors. For example: If there were no relationship between the occurrence of mental symptoms and the severity of carbon disulphide poisoning in all people who might have been subjected to our tests, it would have been unlikely (less than five chances in 100) that we would find the connection established between these two factors in our sample. A probability of 0.05, i.e., of one in 20, or less, is taken to be significant by Fisher and most other statisticians (see R. A. Fisher, Statistical Methods for Research Workers).

Table 2, B 1–3, indicates that a significant association between the estimated severity of disease and the various pathological signs exists only in reference to disturbances of the peripheral nerves, abnormal electrical irritability of the nerve-muscle apparatus and psychic signs. In other words, retrospective evaluation suggests that peripheral neuropathy and mental behavior were the most important of the factors studied in grading the severity of our 120 cases and should be considered as such in the future.

Tabulation of the frequency of clinical signs—such as ataxia, Romberg, pyramidal and extrapyramidal signs, decrease of pupillary and corneal reflexes and the electrical irritability of the finger extensors and flexors and peroneal muscles—in the various groups of severity shows an interesting phenomenon. The first four of the above mentioned signs were found in 6.4 per cent to 21.3 per cent of the 47 persons considered as mildly affected by CS_2. Tenderness of the nerve trunks to pressure and tremor were the most frequent signs in this group. The frequency with which these signs were encountered increased—as could be expected—in the groups of more severely affected workers.

However, pupillary and corneal reflexes as well as electrical irritability of the nerve-muscle apparatus behaved differently. A pathological reaction of the pupils to light was present in 39.2 per cent of 34 mildly affected indi-

viduals. This frequency did not vary by more than 5 per cent in the groups containing cases of greater severity. To give another example, decreased electrical irritability of the finger extensors was found in 62 per cent of 47 workers in the mildest group, decreasing to 50 per cent in the next two groups and reaching 66.6 per cent in the 10 persons most severely affected.

In other words, the number of persons showing one of the first four signs increased with the higher degree of severity of CS_2 absorption, while the number of persons showing abnormal pupillary and corneal reflexes or electrical irritability remained almost the same from the group of the mildest to that of the severest cases.

TABLE III

Mean (M) and Standard Error (SE) of Percentage of Difference of Illumination Required to Elicit Pupillary Reactions and of the Strength of a Jet of Air Required to Elicit Corneal Reflexes in Normal Individuals and in CS_2 Workers Grouped According to Various Degrees of Severity (S).

N = Number of Observations. r = Correlation Coefficient. P = Probability.

S	Pupillary Reflex N	M SE	Corneal Reflex N	M SE
Normal	138	4.6±0.07%	148	0.42±0.02 mg./mm.²
I	34	7.7±0.41%	76	0.49±0.04 mg./mm.²
II	31	8.9±0.64%	39	0.63±0.07 mg./mm.²
III	19	9.8±1.32%	26	0.78±0.08 mg./mm.²
IV	8		6	1.05
	r = + 0.96			+0.97
	P = 0.04			0.007

Decrease of pupillary and corneal reflexes and of electrical irritability of the nerve-muscle apparatus has been determined in figures permitting computation of their mean and standard error in each of the four groups of severity. Table 3 shows clearly the rectilinear, significant progress of the decrease of function from normal over groups I to IV.

The same holds true for the increase of electrical underexcitability of the finger extensors from normal values over groups I to IV which is significant

TABLE IV

Mean (M) and Standard Error (SE) of Electrical Underexcitability of Three Muscle Groups in Normal Persons and in CS_2 Workers Grouped According to Various Degrees of Severity (S)

N = Number of Observations. r = Correlation Coefficient. P = Probability.

S	Finger Extensor N	M SE	Flexor M SE	Peroneal Muscles M SE
Normal	40	7.7±0.12√μC	4.8±0.13√μC	4.5±0.11√μC
I	47	11.8±0.38√μC	9.0±0.33√μC	6.6±0.24√μC
II	34	13.5±0.65√μC	9.3±0.23√μC	10.7±1.06√μC
III	25	15.8±1.18√μC	(6.5)	7.3±0.27√μC
IV	9	18.9±0.77√μC		9.9±0.9√μC
	r=+0.99		+0.89	+0.81
	P=0.001		>0.1	>0.1

whether we compute the difference of the means from group to group or the correlation coefficient over the whole range (table 4). A similar increase of electrical excitability can be demonstrated for the finger flexors and the peroneal muscles, but this increase is not significant.

These computations strengthen the clinical impression, namely, that examination of the pupillary reaction to light with the aid of the Hess pupilloscope, of the corneal reflexes * with the help of graded jets of air, and of the electrical excitability of the common finger extensor by determining its strength-duration curve, are the most accurate and rapid methods of estimating the degree of CS_2 absorption and the damage done to the nervous system, if CS_2 is known to be the noxious agent. The first two methods are, in addition, so simple that they may be applied by a technician in industrial routine examinations.

Discussion

CS_2 is one of the best fat solvents. The conclusion was obvious, therefore, that it dissolves in the myelin sheaths of the nerve fibers just as it was assumed that alcohol acts in this way upon the nervous system (Mattei and Sédan [18]). As far back as 1877 Binz [19] had compared the effect of CS_2 upon the nervous system to that of alcohol and also of chloral and chloroform. This relationship had already been suggested by Simpson [20] when he used CS_2 in 1848 as a gaseous anesthetic for amputation of the breast before he finally recommended chloroform as the best narcotizing agent. This behavior, which was later confirmed by Lehmann,[21] permits little doubt that CS_2 acts as a narcotic upon the surface membranes of the brain cells.

However, this is only one side of the problem. Carbon disulphide, in contrast to chloral and chloroform, has a noxious effect upon the peripheral nerves, the first signs of which may appear as late as four days after the actual intoxication has ceased (MacGregor [22]). In our animal experiments these signs were observed in the fourth week after the onset of the intoxication (Lewey et al.[23]). This delay in the development of the peripheral neuropathy, in contrast to the immediate effect of CS_2 on the hemispheres, raised the question as to whether another link might be intercalated between the CS_2 absorption and the lesions in the spinal cord, brain stem, or peripheral nerves. This hypothesis is strengthened by the fact that no statistical association has been found between the appearance of the psychic symptoms and brain stem or peripheral nerve signs. A further suggestion of a difference in the mechanism of action in acute and chronic CS_2 absorption might be seen in the observation that the number of persons with mental symptoms increased gradually from the group of the slightest to that of the severest cases; whereas the number of persons with involvement of the peripheral nerves was almost the same in all four groups but showed an increase in the severity of the neuropathy. All these considerations suggest that the mecha-

* Corneal scars due to H_2S in spinning room workers should be taken into consideration.

nism through which CS_2 acts on the hemispheres is different from that effective in the rest of the nervous system.

Such a dualistic action in the acute and chronic effects of alcohol is believed to be an established fact today. If the dualistic action recognized in alcohol may be justifiably extended to CS_2 its effect should not be regarded any more as a direct lipolytic effect on the myelin but, similar to that of alcohol, as a neuropathy in consequence of thiamine deficiency.

In fact, histopathological examination of the peripheral nerves in CS_2 intoxication shows that the axis cylinders of the peripheral nerves disintegrate first while the myelin sheath is still in a fairly good condition (Alpers and Lewey [11b]).

Evidence has been given that in CS_2 absorption the thiamine excretion in the urine is markedly decreased and that treatment with thiamine rapidly improves the peripheral neuropathy. Finally, our animal experiments with CS_2 show that daily injections with thiamine delay the development and the death of the animals.

We may go one step further. We have previously stated our reasons for assuming that involvement of the liver and depletion of its stock of vitamin B appear to be one of the essential factors in the occurrence of neuropathy.[17] Furthermore, we have known for a long time that carbon tetrachloride, another excellent fat solvent, produces severe liver damage, and that the onset of the pathological signs in this intoxication is accelerated by a diet rich in fat. Carbon disulphide shows in our animal experiments a similar relationship. These experiments suggest, in addition, that poisoning of coenzymes active in nerve metabolism may be another important factor in the occurrence of neuropathy in CS_2 intoxication.

If these considerations are confirmed it appears that an adequate diet, especially in the cafeterias of plants using CS_2, may prove helpful in the task of preventing CS_2 intoxication. It is only proper to give credit to Delpech [24] who, in 1856, recommended a regimen rich in lean meat—a very unusual diet in France—as the most effective precautionary measure for workers in rubber plants.

Summary

1. This is a report of the neurological and medical findings in 120 viscose rayon workers exposed to various degrees of chronic carbon disulphide (CS_2) absorption. With three exceptions, all these men were at work.

2. Chronic CS_2 absorption may involve all parts of the central and peripheral nervous system. CS_2 absorption is initiated by psychic symptoms later accompanied by peripheral neuropathy and diseases of the cranial nerves, decrease of corneal and pupillary reflexes, as well as by pyramidal and extrapyramidal signs. Varying degrees of Parkinsonism have been observed and, in three persons, a true thalamic syndrome.

3. Subjective and objective symptoms and signs of cardiovascular disease were found in one-fourth of the subjects examined. Arterial hypertension was observed in an unusually great number of young individuals. The mean of the total serum cholesterol values was found 34 per cent above normal with a simultaneous decrease of the values of the cholesterol esters.

4. Graphs illustrate the frequency of signs and symptoms. Some of the pathological signs become more frequent from group to group; others do not, but become severer instead.

5. The hypothesis is proffered that the mechanism of chronic CS_2 absorption is different from that of acute CS_2 intoxication. The first is attributed to thiamine deficiency, possibly by way of a liver damage and by direct poisoning of the coenzymes of nerve metabolism and respiration whereas the second is compared with the narcotic effect of other gaseous anesthetics.

6. The importance of a diet rich in vitamin B in the cafeterias of plants using CS_2 is suggested.

I wish to express my appreciation to the Department of Labor and Industry of the Commonwealth of Pennsylvania and my gratitude to all who have coöperated in this survey.

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THE SOLUBILITY OF ACETYLSULFAPYRIDINE AND ACETYLSULFATHIAZOLE IN THE URINE *

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Shortly after the introduction of sulfapyridine into clinical medicine, hematuria was described as one of the common and dangerous complications of this type of therapy. Acetylsulfapyridine was demonstrated as the excretory form of the drug,[1, 2, 3] and the relationship between crystals of acetylsulfapyridine in the urine and hematuria was quickly recognized.[4, 5, 6, 7, 8]

This work was begun to record the solubility characteristics of acetylsulfapyridine and to determine the type and the amount of urine necessary to effect complete solution of this material. Our method was as follows: a portion of urine was concentrated to a specific gravity of 1.030. Aliquots were taken and adjusted to varying pH between 5.5 and 8.0 by electrometric titration. These samples were further treated with distilled water so that for each different pH range a set of specific gravities from 1.005 to 1.030 was set up. A small amount of each of these solutions, to which had been added an excess of powdered acetylsulfapyridine, was incubated at body temperature for one hour, occasionally shaken and then filtered. The concentration of sulfapyridine in each solution was then determined by the method of Bratton and Marshall after acid hydrolysis (using N-(1-naphthyl)ethylenediamine dihydrochloride in the coupling reaction).[9]

The results of our determinations of the concentration of acetylsulfapyridine in urines of different pH and specific gravities is seen in chart 1. Each graph represents a determination at the specific gravity indicated: 1.005, 1.010, 1.015, 1.020, 1.025, and 1.030. The concentration of acetylsulfapyridine in milligrams per cent is plotted on the ordinates and the pH on the abscissae. It appears from chart 1 that a change in solubility of the drug occurs with the changing pH. There is some tendency for this to represent a straight line function, but it is quite apparent that the concentration varies little on the acid side of neutrality. As soon as the pH of 7.0 is reached, the solubility curve rises sharply. In actual values, the concentration of acetylsulfapyridine below a pH of 7.0 is between 20 and 30 milligrams per cent and above a pH of 7.0 between 30 and 40 milligrams per cent.

Although it is not possible to predict the solubility characteristics of chemical substances, it was quite unexpected to find the solubility of the acetylsulfapyridine to increase as the specific gravity of the urinary solutions

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increased. This is illustrated in chart 1. If the solubility curves plotted are superimposed upon a single graph, there is obtained a series of almost parallel lines, one staggered above the other, with the solubility curve at a

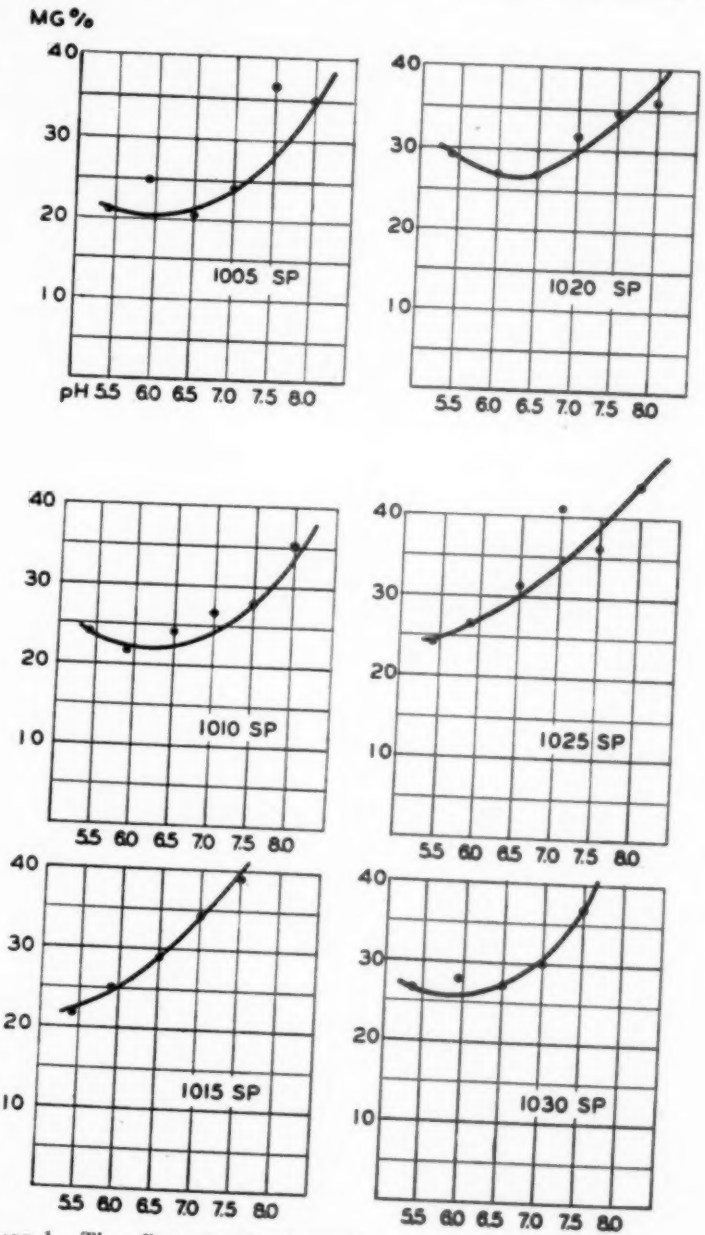

CHART 1. The effect of pH and specific gravity on the solubility of acetylsulfapyridine in urine.

Each graph represents the solubility in milligrams per cent of acetylsulfapyridine at the specific gravity indicated. SP = Specific Gravity.

specific gravity of 1.005 below, and a curve falling between the solubility curves 1.025 and 1.030 above.

Of the several urinary constituents, urea was suspected of playing some rôle in the phenomenon observed. We accordingly repeated our earlier observations, using a urine of low specific gravity (1.005) and sufficient amounts of concentrated urea solution to increase the specific gravity to the levels 1.010, 1.015, 1.020, 1.025, 1.030. Chart 2 shows the results of this

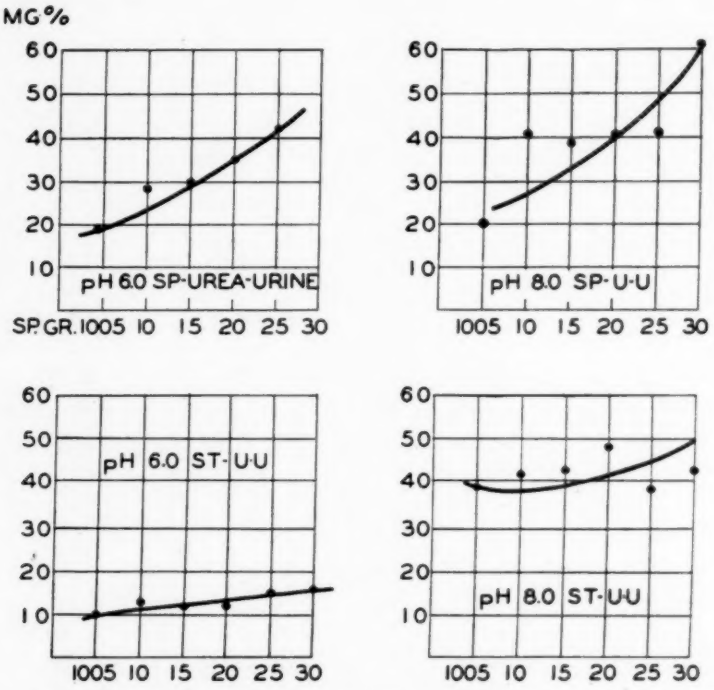

CHART 2. The effect of pH and increasing concentration of urea on the solubility of acetylsulfapyridine and acetylsulfathiazole.

SP = Acetylsulfapyridine.
ST = Acetylsulfathiazole.
U–U = Urea-Urine Solution.

series of determinations. Concentration in milligrams per cent is plotted on the ordinates and specific gravity on the abscissae. The figures above are those of acetylsulfapyridine and below those of acetylsulfathiazole. Those on the left are for a pH of 6.0, and on the right for a pH of 8.0. It is again evident that the solubility of acetylsulfapyridine increases with the specific gravity and with alkalinity. In this particular group of experimental data, solubility is proportional to increasing amounts of urea. The solubility of acetylsulfathiazole is much more marked in alkaline than in acid solutions as compared with acetylsulfapyridine, but increasing amounts of urea seem to affect its solubility little. Other non-reported data confirm this finding.

To determine finally just what effect an increase in specific gravity itself would have, exclusive of any urea effect, we repeated these observations with aqueous solutions of urea and dextrose to which was added acetylsulfapyridine. The results are shown in chart 3. The marked solvent effect of increasing amounts of urea is apparent. On the other hand, the solutions with dextrose show relatively no change in solubility with increasing amounts of solute. Urinary solutions show this effect in a more striking manner.

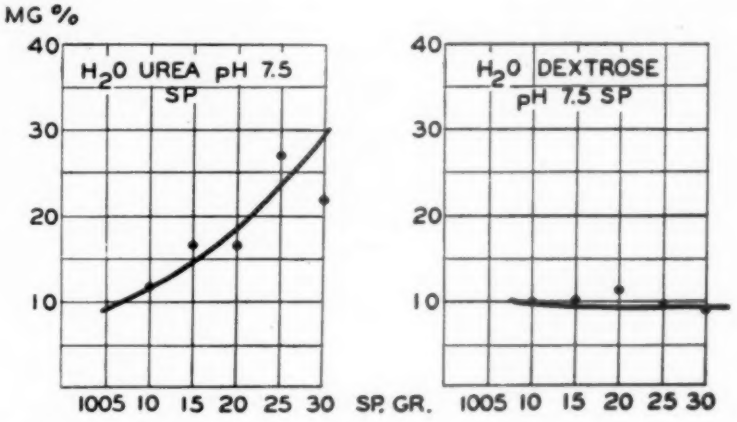

CHART 3. The effect of increasing concentration on urea and of dextrose on the solubility of acetylsulfapyridine in aqueous solution.

Volume ratios for urines of specific gravities 1.005 and 1.030 are 2.5 : 1. The clinical advantage of either specific gravity depends upon the relative solubility of acetylsulfapyridine at that specific gravity. Although the solubility of acetylsulfapyridine at a specific gravity 1.030 may be appreciably greater than its solubility at a specific gravity 1.005, it is not two and a half times the solubility in the latter solution. Accordingly, from our studies, the greater volume of the more dilute urine is more desirable.

Common dosages of sulfapyridine lie between 2 and 6 grams a day. An average figure for the absorption of sulfapyridine is about 50 or more per cent.[8, 10, 11] The urinary excretion of either the free or combined form is almost quantitative for the amounts absorbed.[8] It has been further shown that the urinary excretion of the conjugated drug is about 50 or more per cent.[8, 11] This means that at least one-quarter of the oral daily dose is excreted in the urine as acetylsulfapyridine. If the daily oral dose of sulfapyridine is two grams, about 500 milligrams would be excreted as the acetylated form in the urine. If the daily oral dose of sulfapyridine is six grams, 1,500 milligrams would be excreted as the acetylated form in the urine. In an acid urine of low specific gravity acetylsulfapyridine is soluble to about 25 milligrams per cent. To prevent acetylsulfapyridine crystals from forming in this type of urine a urinary output of 2,000 c.c. would be necessary

for a two gram daily intake, and 6,000 c.c. for a six gram daily intake. On the other hand, with an alkaline urine, the solubility is about 40 milligrams per cent and the urine output necessary for solution of the acetyl form of the drug would be decreased to 1,250 c.c. for a two gram daily dose, and 3,750 c.c. for a six gram daily dose (chart 4).

Dose	Absorption Excretion	Excretion Acetylated (50%)	pH <7.0 Urine Volume 25 mg.% Soln.	pH >7.0 Urine Volume 40 mg.% Soln.
2 gm.	1 g.	500 mg.	2000 c.c.	1250 c.c.
6 gm.	3 g.	1500 mg.	6000 c.c.	3750 c.c.

CHART 4. Urine volume necessary to effect complete solution of acetylsulfapyridine with pH less and greater than 7.0.

The solubility of acetylsulfathiazole shows a much more marked response to acidity and alkalinity changes than does acetylsulfapyridine. In a urine of specific gravity 1.005 at a pH 5.5–6.0, this material is soluble in amounts less than 10 milligrams per cent. If this is compared to the solubility of acetylsulfathiazole in a similar urine at a pH of 8.0–8.5, where the solubility is between 30–40 milligrams per cent, a 300 to 400 per cent increase in solubility is present.

We do not wish to discuss the problem of how hematuria is produced by the sulfonamide compounds, but we have assumed, from the many reports, that when it does occur, it is a result of trauma to the genito-urinary tract by the acetylated form of the drugs that produce it.

There is increasing evidence that some conjugation other than the acetyl form occurs.[2] Glycuronate [12] excretion is so far indicated. Just what proportion of total excreted drug may occur in these forms has not been determined.

SUMMARY

1. To prevent the precipitation of acetylsulfapyridine and acetylsulfathiazole crystals in the urine, the fluid output must be sufficient to hold all of these compounds in solution.

2. The solubility of both acetylsulfapyridine and acetylsulfathiazole is greater in an alkaline urine than in an acid urine, so that enough base should always be taken with these drugs to keep the pH of the urine alkaline.

3. Urea seems to have some importance in the solubility of acetylsulfapyridine in the urine.

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ARSENICAL SENSITIVITY AND VITAMIN C*

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WITH the advent of arsenic as a spirochetocide, the physician found that one of his great problems in handling the syphilitic patient was that of avoiding, if possible, the toxic manifestations of this therapeutic agent, or of treating them if they appeared. Numerous improvements in arsenical preparations and improvements in the technic of their administration have not yet eliminated these problems. Toxic manifestations take many forms —from the milder gastrointestinal disturbances to the severe hemorrhagic encephalitis—with the intermediate complications of hepatitis, purpura, and arsenical dermatitis occurring all too frequently. In a large antisyphilitic clinic, constant and individual attention must be given to the patient receiving therapy in order to complete his treatment without producing a complication more serious than the original disease. All attempts at finding any agent capable of successfully neutralizing this toxicity of arsenic have failed. Likewise, all agents used in treatment of the complications have been found wanting in efficacy.

Recently there have been several reports in the literature on the relationship of vitamin C and neoarsphenamine sensitivity, both experimental and clinical in character. Chapman and Morrell [1] reported a group of experiments indicating that guinea pigs on a diet high in vitamin C developed marked sensitization reactions to neoarsphenamine, while pigs on low vitamin C diets developed a less marked sensitivity. Contrary to this, Sulzberger and Oser [2] reported marked sensitization reactions in scorbutic pigs. Cormia,[3] also working experimentally with guinea pigs, showed that animals on low vitamin C diets had more intense initial skin reactions to neoarsphenamine than normal controls, and that involution of the lesions was slower. Although the experimental evidence seems to carry an implication, the experimental skin lesions at least are so different from the sensitizations seen in the clinical picture that comparison and evaluation are difficult.

Clinically, the application of this supposed relationship between vitamin C deficiency and arsenical sensitivity has been approached in a limited manner only. Dainow [4] reported beneficial results in treating arsenical dermatitis with cevitamic acid in three such cases. Landfisch [5] observed loss of intolerance to neoarsphenamine in patients previously sensitive after the administration of vitamin C. Lever and Talbott,[6] describing a group of miscellaneous forms of dermatitis treated with vitamin C, saw no improve-

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ment in two cases of exfoliative dermatitis. It was, however, not stated that arsenic was the etiological agent in these two cases.

From this examination of the literature it seems evident that no attempt has been made to investigate intensively the possibilities of vitamin C as a clinical therapeutic agent in this group of complications of arsenical therapy.

Early but unorganized attempts to use cevitamic acid in treating various forms of arsenical sensitivity at this clinic were made with inconclusive but promising results. In 1938 with a suitable method available for plasma vitamin C determinations, more careful observations were begun. One group of previously untreated syphilitics was selected in consecutive order, and vitamin C determinations were made upon the blood plasma. A second group was followed through routine arsenic and bismuth therapy courses with vitamin C determinations. A third group of selected cases was taken from patients showing definite arsenical sensitivity. These patients were followed with plasma vitamin C determinations during their therapy with cevitamic acid.* The problem of selecting cases of unquestionable arsenical sensitivity soon became difficult when the entire group of such cases was pooled. Undoubtedly, the skin manifestations represent the ideal type for study. The time of onset is easy to determine, the patient's subjective progress is easy to follow, and the evidence of recovery cannot be controversial. All cases reported were either referred to the dermatological clinic for confirmation of the diagnosis or were seen in that clinic prior to their treatment in the medical department.

Method

The macro method of Mindlin and Butler [7] was used for the vitamin C determination. The oxalated plasma was obtained and precipitated within 30 minutes after the blood was drawn. All bloods were obtained from patients who had not had any food for at least six hours.

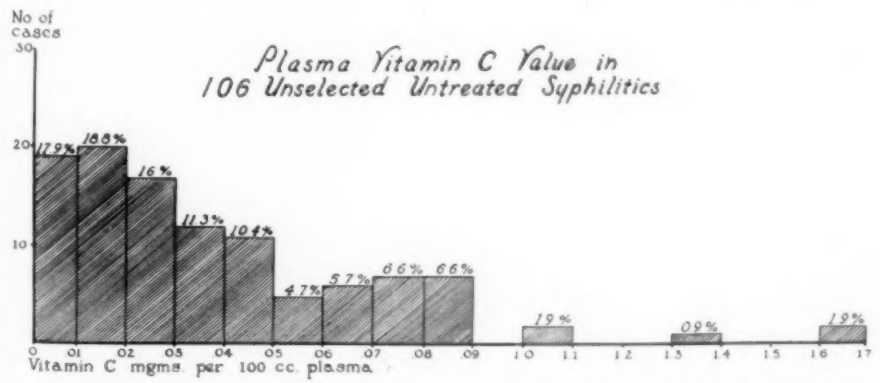

Chart 1. Consecutively chosen and previously untreated syphilitics showing plasma vitamin C levels.

* Cevitamic acid furnished by George A. Breon and Company.

In this group of patients it may be seen that plasma vitamin C levels vary from less than 0.10 mg. per 100 c.c. of blood to 1.4 mg. per 100 c.c. of blood. These represent levels much lower than those usually quoted. A preponderance of the group falls into what has often been called the scorbutic group. It should be pointed out that these patients were attending a charity clinic and that a diet adequate in fresh fruits and vegetables is practically unknown to them. The body weight as an indicator of the state of vitamin C saturation was an untrustworthy guide in this group. The great majority were diagnosed latent syphilis; however, several manifested primary and secondary lesions. No case complicated by other infectious disease was accepted for blood determinations.

Plasma Vitamin C (mg. per 100 c.c.)

Patient Clinical No.	Neoarsphenamine (Total dosage in gm.)							
	0.0 gm.	0.45 gm.	0.9 gm.	1.35 gm.	1.80 gm.	2.25 gm.	2.70 gm.	3.15 gm.
151825	0.21	0.17	0.17	0.33	0.60	0.31	0.72	0.97
162131	0.08	0.05	0.20	0.26	0.13	0.20	0.19*	0.28
162166	0.04	0.12	0.05	0.09	0.36	0.05	0.45	0.70
162890	0.71	0.62	0.68	0.83	0.56	0.89	0.66	0.56
162069	1.64	—	1.26	1.64	0.90	1.06	0.96	1.01
162093	0.18	—	—	0.67	0.54	0.73	0.63	0.48
161967	0.09	—	0.23	0.17	—	0.33	0.04	0.30
162006	0.04	—	—	0.11	0.08	0.15	0.13	0.12
161909	0.14	—	—	0.07	—	0.36	0.37	0.20
158780	0.27	0.21	—	—	0.05	0.47	0.37	—
	(0.34)	(0.23)	(0.47)	(0.46)	(0.40)	(0.46)	(0.45)	(0.51)
Patient Clinical No.	Bismuth (Total dosage in mg. metallic bismuth)							
	0.0	130	260	390	520	650	910	10.40
161500	0.08	0.01	0.15	0.20	0.26	0.50	0.53	0.47
161679	0.05	0.37	0.02	0.11	0.17	0.24	0.10	0.23
161992	0.09	0.08	0.05	0.05	0.32	0.18	0.30	0.54
160778	0.41	0.54	0.74	0.89	—	0.62	0.60	0.59
151231	0.20	0.36	0.31	0.35	0.05	0.85	0.64	0.26
162171	0.49	—	0.22	0.36	0.31	0.44	0.50	0.35
163281	1.04	—	0.83	—	0.90	—	—	0.53
162370	0.26	—	0.24	—	0.12	—	0.55	0.55
161703	0.28	—	0.05	—	0.05	—	0.35	0.32
162842	0.13	0.12	0.11	0.26	0.26	0.24	0.46	—
	(0.30)	(0.25)	(0.27)	(0.32)	(0.27)	(0.47)	(0.45)	(0.43)

* Dermatitis developed.

CHART 2. Plasma vitamin C level before and during routine administration of arsenic and bismuth.

The group shown in chart 2 represented unselected patients, previously untreated, followed for the purpose of determining the presence or absence of a depressing effect of the heavy metals administered upon the plasma vitamin C levels. No such depressing effect is noted. The dietary histories of

these patients indicated clearly a close relationship between the intake of vitamin C and the vitamin C plasma levels.

Arsenical Dermatitis Treated with Cevitamic Acid

The last individually studied group represents five patients with unquestionable arsenical dermatitis. Each was treated with cevitamic acid as indicated in the accompanying summaries and charts. Plasma vitamin C levels were determined before treatment was started and throughout the course of

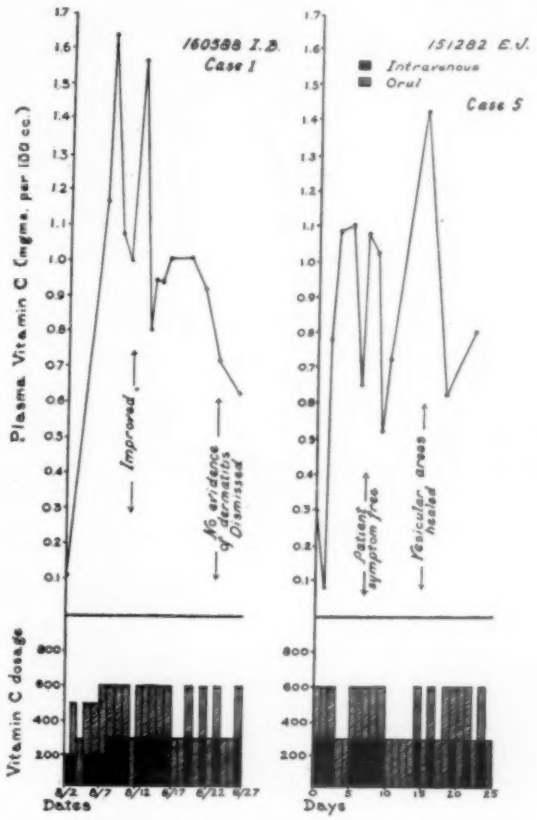

Chart 3. Case 1 and Case 5.

treatment. All patients were treated as ambulant cases; and no therapy other than vitamin C orally and intravenously was administered. Patients were secured from several sources, but all represent a group in clinical classification. Only one patient, case 2, appears in groups one and two. She had vitamin C determinations made before and during routine arsenical therapy. As a group these cases show low vitamin C values, but even in case 2 it is not possible to say that the arsenic therapy had depressed the level to a point where sensitization appeared.

Case Reports

Case 1. I. B. Female, white, aged 32. Entered the medical clinic with complaints of nervousness, stomach trouble, and a positive Wassermann test. Significant in the past history were eight pregnancies with three premature labors, and frequent attacks of upper abdominal pain. The patient was poorly nourished, and had a very severe gingival infection. Otherwise, the physical findings were negative. Roentgen-ray examination with oral dye showed a non-functioning gall-bladder. This patient,

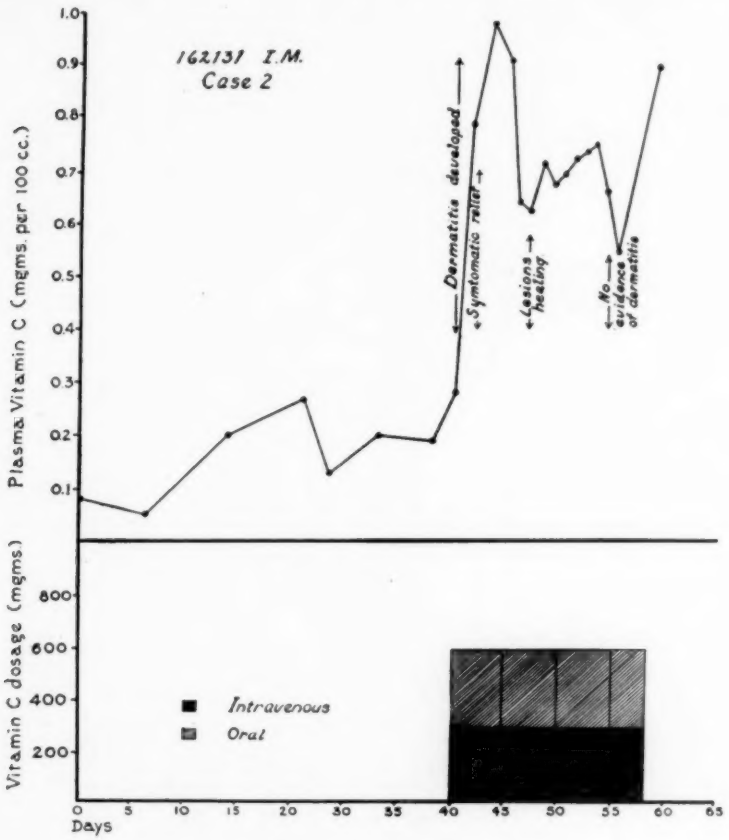

Chart 4. Case 2.

three children, and the husband, living on direct relief, had a weekly allotment of $4.85 for food; consequently, intake of fruits and fresh vegetables was negligible.

After one course of bismuth emulsion consisting of 20 injections of 1 c.c. each, the patient was placed on neoarsphenamine. Following the seventh dose she developed a generalized vesicular eruption, particularly intense on the skin of the face, neck, ears, arms, hands, and trunk. The dermatitis had been present for four days at the time reported. At this time, the patient was placed on cevitamic acid, both intravenously and orally. Within one week the patient was definitely improved. Within three weeks all evidence of dermatitis had disappeared.

Case 2. I. Mc. Female, colored, aged 25. Admitted to the medical clinic with the chief complaint of "bad blood." The patient and her family were on direct relief

and very rarely had any fresh vegetables in their diet. The past history was unimportant. Physical findings were not significant. The medical diagnosis was seropositive latent syphilis.

This patient was placed on neoarsphenamine with an initial dose of 0.3 gram and subsequent doses of 0.45 gram. In this patient plasma vitamin C determinations were being made throughout the course of treatment. Following the seventh injection of neoarsphenamine, the patient developed a typical generalized arsenical dermatitis with marked edema and vesiculation of the skin of the face, ears, neck, extremities, and trunk.

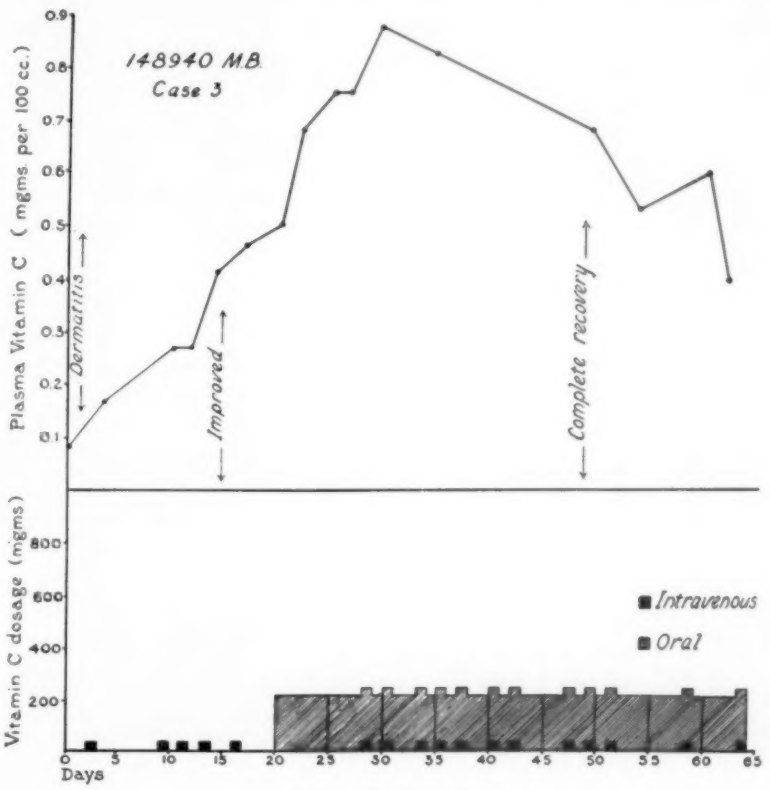

CHART 5. Case 3.

The third day following the onset of the dermatitis, both intravenous and oral cevitamic acid therapy was begun. Within 48 hours the patient had complete relief from the intense burning and itching of the skin; within seven days there was definite healing of the vesiculations; within 14 days the dermatitis had completely disappeared. No other treatment was given during the course.

Case 3. M. B. Female, colored, aged 34. Entered the medical clinic with the chief complaints of nervousness and palpitation. Routine examination revealed that the patient had a positive Wassermann test, but no other significant findings. The family was on direct relief and records of other members of the family indicated definite lack of proper nutrition.

The patient was referred for syphilitic therapy and she received one course of neoarsphenamine, one course of bismuth, and six injections of neoarsphenamine in her

second course of treatment, at which time she developed a typical arsenical dermatitis with generalized involvement of the skin. Treatment with cevitamic acid intravenously was begun. The patient received 50 mg. doses three times weekly. Although we now know the dosage to be quite inadequate, at the end of two weeks' time the patient was showing very definite improvement. She did not show complete recovery until seven weeks had elapsed. It was quite impossible to persuade the patient to take daily doses of medication, and sometimes there were intervals of one week between treatments.

Case 4. W. W. Male, colored, aged 38. This patient entered the dermatological clinic with the chief complaints of burning skin and dermatitis. Onset of the illness had occurred two months previously following the sixth intravenous injection of neo-

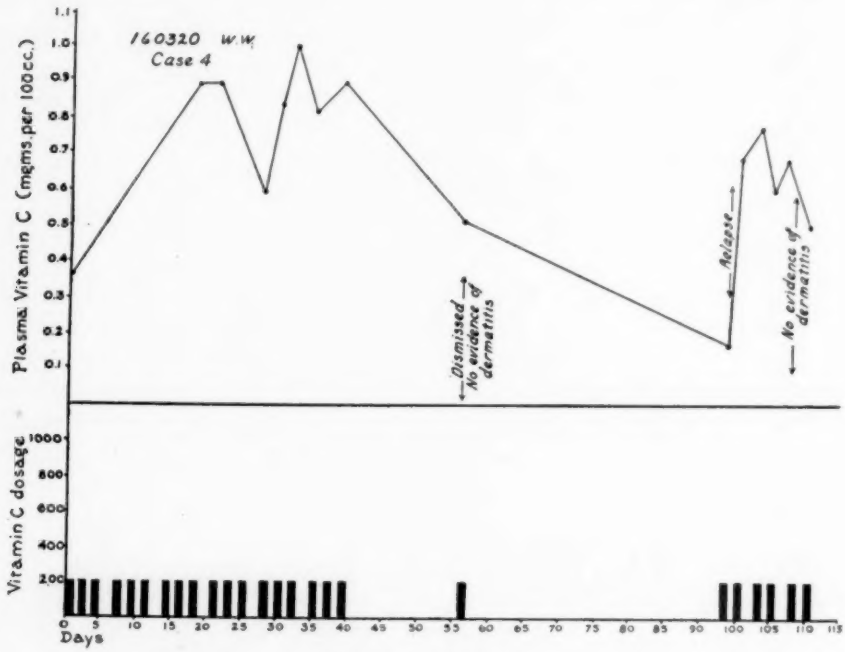

CHART 6. Case 4.

arsphenamine. The patient was not syphilitic, and had been receiving the medication, apparently, for its tonic value. The history did not reveal any inadequacy in the patient's diet. During the two months intervening since the onset, the patient had used many ointments without benefit. A diagnosis of arsenical dermatitis was evident.

This patient was placed on intravenous cevitamic acid in doses of 200 mg. three times weekly. After the sixth dose, the patient showed improvement and was free from the intense burning and itching. With the twelfth dose the dermatitis disappeared. After the nineteenth dose, the patient was dismissed, but returned five weeks later with a mild recurrence. Medication was resumed with a prompt remission. He was again dismissed. Three weeks following his second dismissal he had another mild recurrence which was promptly controlled upon resumption of the cevitamic acid medication.

Case 5. E. J. (see chart 1). Male, colored, aged 18. This patient was admitted to the dermatological clinic with the chief complaints of burning and itching

of the skin. The dermatitis had been present one week, and followed the fifth dose of neoarsphenamine in his third regular course. The patient's nutritional state was good. In addition to syphilis the patient had an active gonorrheal proctitis. The diagnosis was typical arsenical dermatitis of an extremely severe type. Skin involvement was very extensive and associated with marked subjective symptoms. Cevitamic acid therapy, both intravenously and orally, was begun immediately. No other treatment was given. On the seventh day of treatment the patient was free of all the burning and itching of the skin, and all the edema had vanished. Slight vesiculation still remained. By the fourteenth day of treatment the patient was completely symptom free. All vesiculation had disappeared. However, his treatment was continued for fear of relapse.

Discussion

It seems likely that our conception of normal vitamin C values needs downward revisions. In the 106 patients studied previous to the administration of antisyphilitic therapy, values ranging from less than 0.10 mg. per 100 c.c. of blood to 1.4 mg. per 100 c.c. of blood were found. Fifty per cent are below 0.4 mg. No patient evidenced clinical scurvy, yet the values are definitely within the assumed range for such a state. Lever and Talbott [6] found in a group of healthy medical students and nurses 11 per cent showing vitamin C values less than 0.3 mg. Seven out of eight of their patients with exfoliative dermatitis had vitamin C values less than 0.3 mg. Friend and Marquis [8] reported the vitamin C level in one case of arsenical dermatitis at 0.13 mg. per 100 c.c. of blood. Croft and Snorf [9] found 38 per cent of a group of medical patients with vitamin C values less than 0.4 mg. per 100 c.c. of blood. Compared with these available figures the values in this studied group do not seem abnormally low.

No explanation has been made in the past for what is supposed to be relationship between vitamin C deficiency and arsenical sensitivity. None can be offered here for what seems to be a beneficial effect from vitamin C administration in arsenical sensitivity. The problem requires more extensive clinical observation and deeper probing into the basic problems.

There is still no proof for the belief that a method is available for selecting by routine plasma vitamin C determinations a patient who will develop arsenical sensitivity. Case 2, by chance, was being followed at the time of the appearance of the sensitization, but her values had been consistently low. It cannot be said that the arsenic had produced any loss in vitamin C level, yet she improved dramatically with a forced rise in plasma vitamin C levels. The significance is not clear.

While all cases of dermatitis studied show low vitamin C values, the disease was manifest at the time of the determinations. The low values do agree with meager information available in the literature.

Contrary to the findings of Farmer, Abt, and Arons [10] the cases in this group receiving arsenic show nothing which can be interpreted as a depressing effect of arsenic upon the vitamin C levels. Our results agree with theirs in regard to bismuth.

Case 4 is interesting in that the height of his vitamin C level apparently paralleled his state of well-being. Twice, when therapy was stopped vitamin C values dropped, and simultaneously the patient relapsed with a return of his dermatitis. Voluntarily, the patient returned requesting more vitamin C.

No cases have been treated exclusively with oral medication, so no opinion is justified, but the impression has been gained that intravenous administration is the procedure of choice. Dosages in the cases studied have varied with earlier cases getting smaller doses as indicated, and later cases receiving up to 300 mg. intravenously daily. Larger doses may be justified.

Summary

One hundred and six cases of untreated syphilis showed vitamin C levels consistent with their dietary intake of vitamin C. No change in the curve of plasma vitamin C levels was noted in either group of patients receiving the metals arsenic or bismuth. A group of five cases manifesting arsenical sensitivity was studied. Although patients developing sensitivity had low vitamin C values, a low vitamin C value does not necessarily predict such an outcome. Cases of arsenical dermatitis treated with cevitamic acid showed sufficiently favorable response to warrant further employment and study of cevitamic acid therapy.

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CASE REPORTS

LONG STANDING PRODUCTIVE COUGH AS CHIEF CLINICAL MANIFESTATION IN MITRAL STENOSIS; A CASE COMPLICATED BY THROMBOSIS OF LEFT AURICLE*

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In most cases of mitral stenosis with failure, cough is one of a number of symptoms: in few does it overshadow all others. It may be due to chronic congestive catarrh of the bronchial mucosa, but in the case reported below the mildness of the pulmonary changes offered no explanation of the cough. Indeed in this case the absence of marked pulmonary congestion is a crucial point since it aids in establishing the fact that severe and productive cough in this condition can be due merely to the mechanical pressure of an enlarged auricle on the trachea and bronchi.

Case Report

The patient, a 52 year old housewife, was first seen at the Middlesex Hospital Cardiac Clinic, where she was admitted on February 2, 1935 with the chief complaint of severe paroxysmal cough. Her mother had died of "heart disease and asthma." The patient had had rheumatic fever at 19 years and frequent joint pains thereafter. Menopause occurred at the age of 44. She was married for 34 years and had borne eight children, besides having two miscarriages.

In 1934 (one year before admission to the clinic), she had first noted cough, dyspnea on exertion, orthopnea requiring three pillows at night, and loss of weight. The cough was severe and came in paroxysms. For several weeks it had been accompanied by expectoration of thick tenacious mucus. The attacks were more frequent at night. For this condition the patient was admitted to the Middlesex Hospital where she remained for 30 days. Rheumatic heart disease with mitral stenosis and auricular fibrillation was found. She was treated by bed rest, digitalis and ephedrine. Both nurses' and internes' notes recorded the severe exhausting cough and "continuous expectoration." At this time impaired resonance was noted at both bases and throughout both lung fields anteriorly and posteriorly; numerous sibilant and sonorous râles were present. Stereoscopic radiographs were taken of the chest on December 26, 1934. The report was as follows: "The apices aerate fairly well. The appearance is that of generalized fibrosis of both lung fields with some pulmonary edema and pleural effusion in the left base. There is no evidence of pulmonary tuberculosis. The heart is mitral in type. There is a suggestion of bronchiectasis in the right base."

On physical examination we observed a middle-aged woman in a poor state of nutrition, weight 125 pounds, temperature 98.4° F. Skin and mucous membranes were pale but not cyanotic. All teeth had been removed. The neck showed no masses and

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no abnormal pulsations. The heart was enlarged to the left with the apex impulse in the anterior axillary line. The sounds were weak, irregular, rapid and no murmurs were detected on this examination. Later a long, rumbling diastolic murmur was heard in the mitral area and a short systolic one in the left third and fourth interspaces. The second aortic and pulmonic sounds were equal. Peripheral vessels were somewhat sclerotic. The blood pressure was 120 mm. of Hg systolic and 80 mm. diastolic. The chest showed dullness at the apices, especially on the right, but no râles were present. The abdomen was slightly distended and the musculature flabby. The liver was not enlarged. Fluoroscopic examination showed a generally enlarged heart with fullness along the left border in the region of the pulmonic conus and left auricle. Enlargement of the right auricle was suggested by the increase of the heart shadow to the right of the midline.

The urine was acid, specific gravity was 1.011; there was a trace of albumin, but no sugar; an occasional white blood cell was seen microscopically. The Wassermann test was negative. The hemoglobin was 68 per cent (Sahli), red blood cells 3,860,000, white blood cells 7,400, polymorphonuclears 70 per cent, lymphocytes 22 per cent, eosinophiles 2 per cent, and basophiles 1 per cent. The sputum examination was negative for tubercle bacilli and for blood.

The diagnosis made was as follows:

(1) Rheumatic heart disease—inactive.
(2) Mitral stenosis and insufficiency with enlargement of both auricles.
(3) Auricular fibrillation.
(4) Possible bronchiectasis and lung fibrosis.

Following the first clinic visit, the patient had an upper respiratory infection and with it came increased cough which was so severe as to cause loss of appetite and several episodes of vomiting. This symptom was not helped by cough syrups but subsided with rest in bed and digitalis. In May 1935 the cough returned and the patient noted blood-streaked sputum for the first time. Her heart rate was controlled by digitalis at approximately 76, without pulse deficit. She was free from other symptoms. During the next two years, the patient remained ambulatory and had short periods free from cough interspersed with others when this symptom was severe. She was treated with potassium iodide solution, with ammonium chloride, and with various cough mixtures, besides the daily maintenance dose of 0.1 gram of digitalis.

In June 1937 cough and expectoration were again troublesome. Postural drainage was unsuccessful. The patient was referred for bronchoscopic examination and treatment. The bronchoscopist reported that the case appeared to be "an early stage" of bronchiectasis without evidence of any dilatation of bronchi. Mucus was removed by lavage and the patient felt clinically improved so that she requested further treatment. Expectoration stopped for three months. A total of seven bronchoscopic treatments was given during the next six months; thereafter the patient refused such treatments as she felt weakened thereby.

In June 1938, edema of the legs was first noted. As the patient had severe varicosities, these were thought to account for at least part of the swelling. Râles were present at the left base. The patient was urged to remain off her feet and digitalis was increased to 0.2 gram daily, since the pulse rate varied from 88 to 100 per minute. After temporary improvement, edema of the legs again became marked in January 1939, and was accompanied by severe dyspnea, by orthopnea and by cyanosis. The cervical veins were engorged. Coarse râles and dullness were present at both bases; the heart was irregular (120) with pulse deficit. Sacral edema was also present. The patient was again admitted to Middlesex Hospital and a diagnosis of congestive failure made. Urea nitrogen was 14.1 mg. per 100 c.c. of blood; sugar 121 mg. Salyrgan was given intravenously every two days, and with limited fluids and ammonium chlo-

ride the patient became free from evidence of fluid retention and lost 20 pounds. After a brief remission during which the patient felt well, congestive failure again became evident in March 1939. Again she improved after hospitalization, but cough remained troublesome.

An electrocardiogram on January 1, 1940, showed auricular fibrillation, rate 100; QRS 0.08; right axis deviation; widening and notching of QRS in Lead I and Lead II; ventricular premature contractions in Lead III; T_1 and T_2 upright and T_3 and T_4 diphasic. Circulation time with saccharin was 26 seconds (normal 9–16 seconds). Again the cough was the only complaint during the clinic visits, usually with sputum, occasionally blood tinged. The nurses and physicians of the clinic learned to recognize her coming long before seeing her, because of the loud and nearly continuous cough which heralded her presence. In April 1940, edema of the legs again became marked in spite of the weekly dose of salyrgan.

On July 9, 1940, she walked several blocks to the clinic which she reached by great effort. Her color was ashen gray, and her lips, ears and fingers were markedly cyanotic. She had massive pitting edema of the legs, and was extremely dyspneic and orthopneic. Her pulse was weak, rapid and irregular, and blood pressure readings could not be obtained in either arm. A gallop rhythm was present at the apex. She was admitted at once to St. Peter's Hospital in a moribund condition and she died six hours later.

Autopsy was performed by Dr. S. E. Moolten, pathologist.

Autopsy Protocol

The subject was described as a poorly developed female of 53 showing marked lividity of dependent parts and head. There was considerable soft pitting edema of the lower extremities and sacrum. There was a faint purpuric mottling of the skin of the legs. There was no clubbing of the fingers and no jaundice.

Lungs: Both lungs were adherent over part of their surface especially the left lung which was densely adherent to the diaphragm and fibrous pericardium. The lungs were somewhat firmer than normal in consistence, and on section showed only slight hyperemia of dependent portions. The lowest part of the right lower lobe was somewhat indurated and on section presented a somewhat more anthracotic appearance than the remaining lung and seemed slightly more airless. A similar change was seen in the lower part of the left lower lobe. The remaining tissue was more crepitant throughout and was fairly dry and pale, showing minimal congestion and no significant edema. The trachea was of normal size. However, the right main bronchus was somewhat wider than normal for a short distance and the left main bronchus was slightly diminished in caliber and seemed somewhat elongated. The distance from the carina to the orifice of the right upper lobe bronchus was 2.5 centimeters and from the carina to the left upper lobe bronchus was 4.5 centimeters. The right main bronchus was approximately 1.7 centimeters in diameter and the left main bronchus 1.2 centimeters. The branches of the right main bronchus appeared normal throughout. Those of the left main bronchus seemed somewhat narrowed as far as they could be dissected and the orifices were somewhat flattened from before backwards in contrast to those of the right bronchus. The mucosa was pale and smooth and of normal appearance. The tracheo-bronchial angle was greatly exaggerated measuring approximately 135°. This was the result of changes in the left auricle which will be described below (figure 1).

Heart: The pericardial cavity was completely obliterated by fibrous adhesions. The outer layer of the pericardium was similarly bound by fibrous adhesions to the overlying lungs anteriorly and laterally, by obliteration of the intervening pleural space in this region. The soft tissues of the upper mediastinum were somewhat thickened. The heart was greatly enlarged as a result of a marked degree of dilatation and a

fairly marked degree of hypertrophy. The wall of the right ventricle was nearly one centimeter thick. The right auricle was also markedly dilated and its endocardium was thickened and more or less opaque and white. The right auricular appendage was somewhat contracted and flattened and contained no thrombi. The superior and inferior vena cavae were somewhat dilated in a uniform manner. The auricular myocardium was moderately atrophic except in its lowest portion where it was hypertrophic. The tricuspid valve showed a moderate degree of hyalin thickening, especially along the line of closure, with some retraction. The chordae tendineae were, for

FIG. 1. Specimen showing widening of tracheo-bronchial angle and enlarged left auricle with thrombus. Note the slit-like mitral orifice.

the most part, considerably shortened and thickened with a considerable degree of fusion near their attachment, and the papillary muscles were shortened. There was a pronounced degree of valvular incompetence. The pulmonic valve appeared grossly normal. The pulmonary artery was smooth and free of atheroma. The left auricle, before opening, could be felt as a peculiar hard tumor mass just beneath the bifurcation of the trachea. When opened this effect was seen to be the result of an adherent mural thrombus occupying the upper two-thirds of the auricular cavity and extending for a short distance into the lumen of the left upper pulmonary vein, causing marked narrowing but not obstructing it completely. The thrombus, in large part, was pale flesh color and gray especially in the deepest portions. It could be separated from its attachment to the auricular endocardium revealing the latter as greatly thickened and somewhat roughened. The auricular myocardium in its upper part was moderately atrophied. In its lower part it was greatly hypertrophied and reached 0.75 centimeter in thickness. There were numerous areas of whitish plaque-like endocardial thicken-

ing and wrinkling throughout the left auricle where it was not in contact with thrombus. The mitral valve was extremely narrow and reduced to a slit about one centimeter long and a few millimeters wide. The mitral leaflets were moderately thickened and hyalinized with areas of calcification. The chordae tendineae were extremely short, thick, and fused, and the papillary muscles were elongated and thickened with fibrosis of the tips. The left ventricle was of normal appearance on section and its endocardium appeared unaltered, the wall was of normal thickness and the cavity contracted. The aortic valve cusps were moderately thickened and the edges were fairly rigid producing a moderate degree of insufficiency. There were no vegetations except a tiny area of projecting fibrinous material on one of these cusps. The aorta was smooth and elastic and presented scattered areas of slight atherosclerosis and was slightly dilated in its ascending portion. The coronary vessels were somewhat diminished in calibre but smooth and free of obstruction.

Liver: The liver appeared slightly contracted rather than enlarged. The surface showed somewhat exaggerated venous markings and was finely granular with considerable wrinkling. It cut with some difficulty revealing considerable exaggeration of the lobules throughout. Some of these were two to three times normal size and others were much smaller. The interlobular tissue was slightly exaggerated and had a pale translucent aspect. The centrolobular areas appeared considerably reddened but most of the blood had run out of the organ. In many of the lobules fine yellow granular areas could be detected on gross inspection. The lobules in general were quite yellowish. The hepatic veins were widely patent and appeared slightly thickened. The portal vein was also slightly thickened and showed slight plaque-like opacities at branchings. The gall-bladder was contracted firmly about a number of small black facetted pigment calculi. There was considerable cholesterosis of the gall-bladder mucosa. The hepatic and common bile ducts were slightly widened in a uniform manner and contained no calculi.

Pancreas: The pancreas was rather firm. The cut section was negative.

Spleen: The spleen weighed 230 grams, was enlarged to a moderate degree and was very firm. It had a rubbery consistence and showed a dark brownish-red cut surface with somewhat exaggerated venous markings. The splenic vein was patent and smooth.

Adrenals: Negative.

Kidneys: Both kidneys were of normal size and were smooth. The capsules stripped readily revealing a slightly congested surface with a few small irregular flat stellate scars extending slightly beneath the surface. On cut section the parenchyma was somewhat congested and firm. The pelves, ureters and bladder were negative. The kidneys together weighed 440 grams.

Genitals: The vagina was smooth and atrophic. The external os of the cervix was occluded by a mucus plug and a fibroadenomatous polyp. The cavum uteri showed atrophic endometrium with superficial hemorrhage. The myometrium was atrophic. The ovaries were shrunken and fibrotic.

Diagnoses:

1. Chronic recurrent cardiovascular disease, rheumatic, with extreme mitral stenosis and moderate aortic insufficiency (Aschoff bodies present).
2. Marked tricuspid insufficiency.
3. Universal adhesion of pericardium.
4. Adherent thrombus of left auricle causing marked reduction of lumen.
5. Elongation and narrowing of left main bronchus.
6. Marked dilatation and hypertrophy of the right ventricle.
7. Marked dilatation of the right auricle.
8. Chronic passive congestion of liver, spleen and gastrointestinal tract.

9. Adenomatous regeneration of hepatic lobules.
10. Stasis catarrh of stomach.
11. Cholelithiasis.
12. Bilateral pleural adhesions.
13. Fibrous induration and atelectasis of basal areas of both lungs.
14. Anasarca.

Histology

Heart: Section through auricular thrombus: thrombus composed of eosin-staining amorphous substance, with numerous areas of spongy rarefaction alternating with more or less homogeneous areas, the latter generally showing a definite lamination. Considerable hyalinization of deepest areas abutting on endocardial region. Attachment of thrombus to auricular wall was marked by irregular collections of hemorrhage, old and recent, within dense hyaline avascular tissue resembling dense collagenous tissue which merged insensibly with overlying hyalinized thrombus. Still deeper

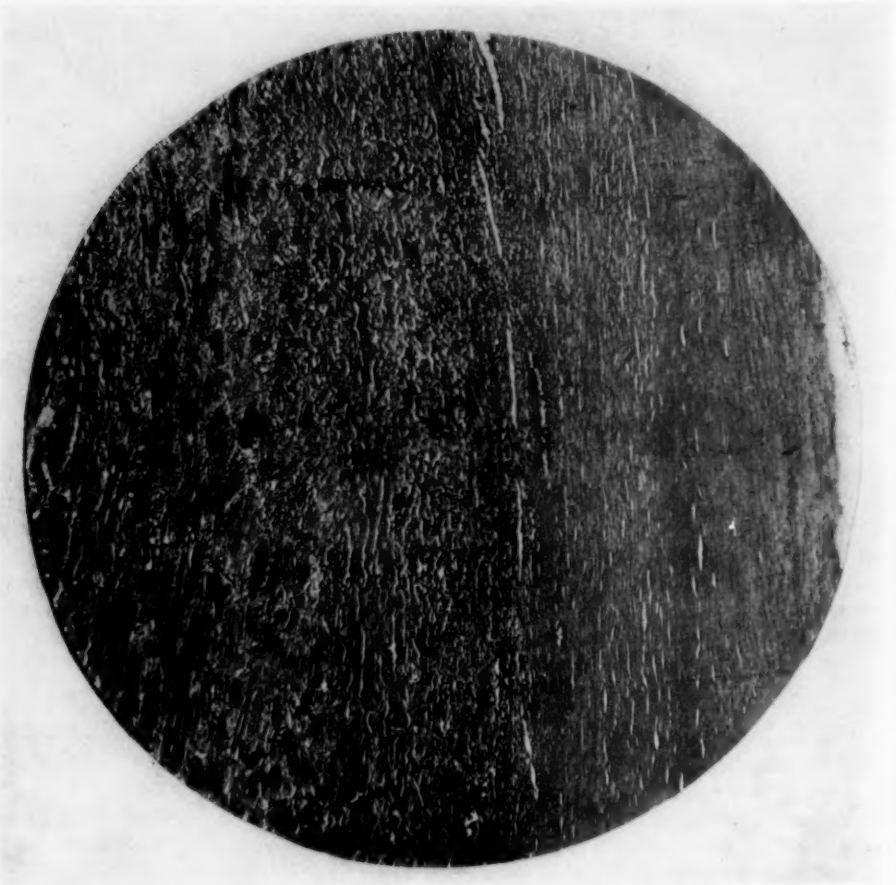

Fig. 2. Section of wall of left auricle showing extensive fibrosis and hyalinization of subendocardial region with considerable replacement of myocardium. Note discontinuity and distortion of remaining muscle fibers.

FIG. 3. Recent Aschoff granuloma within myocardium of left ventricle.

the structure of the collagenous fibrous tissue was more evident as such but showed considerable degeneration, so that many cell nuclei were replaced by empty clefts, others appeared shrunken and pyknotic. This was most marked in a strip overlying a still deeper hemorrhage within the subendocardial fibrous tissue which was of considerable thickness. There was no differentiation into endocardium and subendocardium as such and no endothelial layer could be defined. The dense layer of fibrosis occupies the greater part of the thickness of the auricular wall, and the auricular muscle was discontinuous and largely degenerated except for scattered islands of shortened thickened fibers irregularly disposed and with bulky hyperchromatic nuclei

(figure 2). There was a slight irregular infiltration of this layer with lymphocytes and a variable degree of congestion. The epicardium was considerably thickened by dense fibrous tissue forming a more or less continuous layer, apparently the result of adhesion with the parietal pericardium. Sections through both ventricles and the right auricle showed a few recent Aschoff nodules (figure 3) as well as a number of small areas of scarring representing healed Aschoff nodules; the fibers of the right ventricle and auricle showed well-marked hypertrophy.

FIG. 4. Section of lung showing marked narrowing of branches of pulmonary artery by intimal fibrous hyperplasia. Note patchy atelectasis and thickening of alveolar septa but surprising absence of congestion and edema.

Lungs: The most striking changes in the lungs were the evidences of previous marked chronic passive congestion and the relative lack of congestion at the present time, also the hypertrophy of the intrinsic muscle of the lung and the narrowing of arteries. Previous chronic passive congestion was seen in the form of thickening of alveolar septa as a result of increase in fibrillar reticulum, together with moderate contraction of the alveoli and considerable hypertrophy of the muscularis of the alveolar ducts about the orifices of the alveolar sacs. Numerous areas of old atelectasis were seen with partial fusion of alveolar septa and here the muscle fibers appeared

shortened and thickened and gave rise to the appearance of "muscular cirrhosis." In some sections numerous "heart failure cells" were seen within the atelectatic areas or lining the walls of other alveoli; these contained old blood pigment and anthracotic pigment and often appeared degenerated; in some areas they were secondarily engulfed by multinucleated foreign body giant cells formed by more recent proliferation of alveolar epithelium. The latter was often somewhat hyperplastic, forming rows of cuboidal epithelium in and about areas of atelectasis. Very striking was the lack of blood in the alveolar capillaries, many appearing collapsed and bloodless, others showing only small numbers of erythrocytes; the usual appearance of scalloped projecting capillary outlines engorged with blood was entirely lacking; moreover nowhere was there to be seen any trace of edema fluid or other exudation. The small and medium size arteries showed moderate to marked intimal fibrous thickening with resulting narrowing of lumen, often very marked; the internal elastica seemed somewhat thickened and reduplicated. A few nodules of lymphoid character were seen here and there but no other evidence of leukocytic infiltration. Carnification also was not seen. Bronchi contained some mucus (figure 4).

Liver: Considerable chronic passive congestion with thickening of reticulum framework and mild centrolobular degeneration were noted; there was marked intimal fibrous hyperplasia with narrowing of lumen of branches of the hepatic artery; Glisson's capsule presented considerable fibrosis with subcapsular atrophy and fibrous replacement of lobules.

Spleen: Marked chronic passive congestion with thickening of reticulum framework and beginning fibrosis of pulp cords were noted.

Adrenal: The sinusoids of the cortex and of the medulla showed considerable congestion; the cells were well formed and the layers were of normal proportions; there was slight patchy degeneration of cortex; the surrounding fat tissue showed foamy condensation as seen in fat resorption.

Kidney: The kidney showed uniform congestion of cortex and medulla; glomeruli were numerous, well formed, and congested; Bowman's space was somewhat dilated but free of exudate of cells or protein; the arterioles and small arteries showed no significant changes.

Stomach: There was moderate hypoplasia of the mucosal glands with scattered areas of slight hyperplasia and diffuse congestion and edema of the stroma; there was mild infiltration of the stroma with lymphocytes and plasma cells, also of the submucosa and of the muscularis.

Comment

The left auricle constitutes most of the posterior portion of the heart. The bifurcation of the trachea and part of the left main bronchus lie just above it. Unusual degrees of enlargement of this chamber have been reported in mitral valvular disease associated with marked insufficiency or stenosis and where extensive rheumatic carditis is present in the auricular muscle. By compression of neighboring structures, a number of unusual secondary effects may present themselves clinically.

(1) The upward displacement of the left main bronchus and pulmonary artery may compress the left recurrent laryngeal nerve in its course beneath the arch of the aorta resulting in paralysis of the left vocal cord. This gives rise to hoarseness and "brassy cough" as in the cases of left ventricular failure reported by King, Hitzig and Fishberg.[1] In such cases the lungs may be remarkably free of signs of congestion clinically although the pulmonary veins appear markedly engorged roentgenologically. Hoarseness was not observed in the present case nor were the vocal cords described as abnormal by the bronchoscopist.

(2) Compression of the esophagus in the middle portion of its course behind the left auricle may cause some degree of difficulty in swallowing. In five such cases reported by Nichols and Ostrum [2] dysphagia was a prominent symptom; in one case a tumor of the esophagus was suspected and the patient subjected to gastrostomy. Cough was mentioned in four as one of many symptoms but was not especially prominent. These authors emphasize the relative freedom from congestive heart failure in these cases. A recent publication discusses the occurrence of dysphagia in a variety of disorders of the circulatory system—among them the dilated left auricle.[9]

(3) The chief effect of the dilatation of the left auricle may be seen in the compression of the left main bronchus and widening of the tracheo-bronchial angle as in the case reported above. With such enlargement, the auricle may act as a wedge penetrating the tracheal bifurcation and producing a widening of the angle from the usual range of 50 to 80 degrees to as much as 150 degrees. In this process the bronchi, especially the longer left one, may become considerably compressed. Cough may be an outstanding symptom because of the mechanical irritation of this sensitive portion of the bronchial tree. According to Steele [3] bronchial compression by an enlarged left auricle has been known for nearly a century. Rarely it is sufficiently marked to produce atelectasis of the left lung and chronic inflammation with bronchiectasis. He reviewed the literature from 1838 and presented a case resembling the author's in the severity of the cough, the presence of sputum with blood spitting and the long duration of symptoms (5 years). Here too, bronchiectasis of the left base was suspected; however, on lipiodol injection this was disproved and the distortion of the left main bronchus demonstrated.

Routier and de Balsac [4, 5] presented the radiological findings in such cases and Graybiel [6] reviewed the mechanism of its production.

In the author's case the cough was known to have been present for over six years and was usually productive of mucoid or muco-purulent sputum which was occasionally blood tinged. In the beginning most attacks were initiated by an upper respiratory infection but later persisted without relation thereto. During most of this time the patient was ambulatory and otherwise comfortable, with remarkably good exercise tolerance and relative freedom from signs of congestive failure. The angle at the bifurcation was found at autopsy to be 135 degrees, although the degree of auricular enlargement was not excessive. Clinically the diagnosis of bronchiectasis was considered because of the violence and persistence of the cough, the amount of expectoration, the frequent moist râles at the left base and the beneficial effects of bronchoscopic treatment. However, the patient obtained no relief from postural drainage. Lipiodol studies were not made but the larger bronchi showed no dilatation at bronchoscopy. It is possible that such studies might have been useful in explaining the true mechanism of the cough, by demonstrating the alteration in size and calibre of the left main bronchus and its relation to the heart shadow.

The most serious complication of the rheumatic disease in this patient was the formation of a large pedunculated mural thrombus in the dilated left auricle. This proved to be the actual cause of her death. It has been shown by Graef, Berger, Bunim and de la Chapelle [7] that such antemortem thrombi are fairly common in the left auricle and appendage of a patient with severe mitral stenosis, congestive failure, auricular fibrillation and rheumatic inflammation of the

auricular muscle. All these conditions were fulfilled by our patient whose heart irregularity was already present for an unknown period of time when she was first seen six years ago, and who showed at autopsy a slit-like mitral orifice and outstanding auricular endocardial changes. The possible relation of the mural thrombus in this case to the patient's cough is a matter of speculation. At autopsy the attachment of the thrombus was found to be in the upper portion of the left auricle and it was of tumor-like hardness. It is not improbable that the effective pressure of the enlarged left auricle upon the overlying bronchus was considerably enhanced by the hard thrombus mass in that region.

The terminal clinical picture was marked by peripheral circulatory collapse rather than by congestive heart failure. Her blood pressure was unobtainable, she was intensely cyanosed, and her limbs were cold and clammy. The autopsy indicated that active rheumatic infection was present at the time of death, which accords with the statement of Graef et al.[7] that the persistence of active inflammation appears to be the chief factor in the development of auricular thrombi. Furthermore, there were evidences that the thrombus had undergone considerable recent enlargement through propagation upon its surface. Her final collapse was apparently of rather gradual development instead of sudden development as in cases of ball-valve thrombus of the left auricle in which the thrombus lies free within the cavity of the auricle and produces sudden plugging of the mitral orifice. The latter syndrome was recently reviewed by Aronstein and Neuman [8] who, however, state that the separation of cases of ball thrombus from cases of pedunculated thrombus of the left auricle is of academic interest since the symptoms may be similar. In the present case peripheral circulatory failure was of such marked degree and the volume of blood in circulation so markedly decreased that the lungs appeared practically bloodless at autopsy. Notwithstanding, they showed histological evidences of previous congestion of long duration.

Summary

1. A case is reported in which severe chronic and productive cough was the chief symptom for six years in a woman with mitral stenosis.

2. Auricular enlargement and widening of the tracheobronchial angle to 135° were found at autopsy.

3. The case was complicated by the presence of a large pedunculated thrombus of the left auricle which terminally precipitated circulatory collapse of peripheral type; the latter probably explains the nearly bloodless condition of the lungs and other viscera at autopsy.

The writer wishes to express appreciation to Dr. Sylvan E. Moolten for the autopsy material and for his kind advice and suggestions.

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ASSOCIATION OF POSTURAL HYPOTENSION WITH SYMPATHETIC NERVOUS SYSTEM DYSFUNCTION; CASE REPORT, WITH REVIEW OF NEUROLOGIC FEATURES ASSOCIATED WITH POSTURAL HYPOTENSION *

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The term orthostatic, or postural, hypotension has been applied to a condition characterized by a marked fall in the systolic and diastolic blood pressures when the patient changes from the recumbent to an erect posture. The salient features, besides the orthostatic hypotension, in order of frequency, are: 1. Weakness; 2. Anhidrosis, or hypohidrosis; 3. Increased distress in summer; 4. Greater urinary frequency at night; 5. Variation in pulse rate with change in posture; 6. Loss of libido and potentia; 7. Orthostatic syncope with loss of consciousness; 8. Low basal metabolic rate, — 10 or lower; 9. Blood urea of 40 or more mg. per 100 c.c.; 10. Pallor; 11. Secondary anemia; 12. False appearance of youth; 13. Neurologic signs.

This disorder was first described in 1925 by Bradbury and Eggleston,[1] and the literature, when reviewed in 1936 by Chew, Allen and Barker,[2] revealed a total of 26 accepted cases. Although the number of cases is few, 13 cases have been reported from the Mayo Clinic.[2] It is probable that many cases are overlooked and that many are not reported.

The chief interest in this condition in the past has been in the cardiovascular manifestations. The neurologic features were commented upon by Chew, Allen and Barker,[2] who found neurologic signs in 23 per cent of the cases. This did not include the case reported by Alvarez and Roth [3] in which an undiagnosed illness, with features of a mild encephalitis preceded the onset of the orthostatic hypotension. In the five cases with neurologic signs there were no constant findings.

Case 3 in the report by Bradbury and Eggleston [1] had inequality of the pupils, hyperactive tendon reflexes and a bilateral Babinski sign.

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Ganshorn and Horton [4] reported a patient who had slight ptosis of the upper right eyelid, inequality of the pupils, questionable enophthalmos, slight horizontal nystagmus and some difficulty in articulation. There was slight tremor of the right arm on movement; the abdominal reflexes were absent; the patellar reflex and ankle clonus were increased; the Babinski sign was questionably present; and there was diminished sensibility to the tuning-fork. The gait was somewhat ataxic, and fairly definite positive results were obtained with Romberg's test.

Croll, Duthie and MacWilliam [5] reported a patient with an Argyll Robertson pupil on the left side and with absent patellar reflexes.

In case 5, reported by Chew, Allen and Barker,[2] there was definite evidence of syphilis of the central nervous system. There were Argyll Robertson pupils, a right VI nerve paralysis, loss of patellar and Achilles reflexes, diminution of vibratory sense in the lower extremities and a positive Romberg sign. In case 6 of the same series, the patient had unequal pupils, and the larger pupil would not dilate further when cocaine hydrochloride was instilled in the conjunctival sac. In addition, there was hypoactivity of the anal sphincter. These authors quote Woltman as suggesting that the changes in the central nervous system, occasionally seen in cases of orthostatic hypotension, may be the result of irreversible chemical changes which are caused by deprivation of oxygen that is in turn brought about by the drop in blood pressure during orthostatism.

Ellis and Haynes,[6] in an article on postural hypotension with particular reference to its occurrence in diseases of the central nervous system, report six cases, in four of which there were definite evidences of neurologic disease, and an additional case in which there was some evidence of involvement of the central nervous system. They accept the belief that postural hypotension results from a failure of the normal sympathetic vasomotor reflex to produce vasoconstriction when the subject assumes an erect position. Because of the widespread effect, it was their belief that the site of the lesion is either in a sympathetic center, or in an efferent pathway controlling the entire response, or it is generalized throughout the efferent pathways or nerve endings.

Bickel and Demole [7] have reported a case and have stressed the importance of disease of the central sympathetic centers and pathways in the etiology of the condition.

Interest in the neurologic features of this disorder was aroused by the case to be reported, which showed neurologic changes, and by study of the neurologic features in the previously reported cases. Further stimulation was provided by the report of Ransom, Kabat and Magoun [8] on the autonomic responses to electrical stimulation of the hypothalamus, preoptic region and septum. In certain indefinite regions, it was possible by electrical stimulation to obtain a marked fall in blood pressure and changes in bladder contractility.

Case Report

S. A. J., a 43-year-old minister, was referred to Dr. G. A. Young for examination August 26, 1936, by Dr. H. S. Andrews, of Minden, Nebraska.

The chief complaints were persistent dizziness, weakness in the legs and difficulty in walking, aching pains in the body, and difficulty in urination.

The patient had been perfectly well until about five years previously. At that time he first began to notice difficulty in urination, associated with increased frequency

and some dribbling. A physician had first been consulted three years previously because of burning on urination. This persisted over a period of time, and on January 14, 1935, the bladder difficulty was thoroughly investigated by Dr. Anton Hyden of Sioux Falls, South Dakota. Cystoscopic examination revealed about four ounces of residual urine. The mucosa of the bladder was very much inflamed. Observation of each ureteral meatus showed the urine coming out in slow rhythmic spurts. There was no real obstruction found. The urine from the ureteral catheterization was initially clear, but the bladder urine was found to be filled with pus cells and a great number of colon bacilli. The pyelogram showed only some haziness in the middle calyces of the right kidney pelvis. A cystogram and airogram showed the bladder to be slightly contracted, although on filling it would hold a good amount of fluid. The roentgen-rays showed some reflux into the ureters. The diagnosis was cystitis due to the colon bacillus and some involvement of the nervous system causing a lack of tone of the sphincteric muscles. The cystitis disappeared on treatment with a ketogenic diet. On August 8, 1935, a prostatic resection was done by Dr. Hyden because of protrusion of the lateral lobes of the prostate, in an effort to relieve a possible obstruction, and in the hope that this might provide a greater ease in emptying of the bladder.

For a period of two and one half years prior to examination there had been dizziness on sudden change of position or with exertion. Frequently during that time there were what were described as "nerve aches" in the extremities, particularly during the morning. In addition, there were complaints of tremor of the hands, a lack of sexual desire, an inability to obtain an erection or orgasm.

During the three months before being seen, the patient complained particularly of an unsteadiness in gait and marked weakness of the legs. It was necessary for him to walk slowly to keep from staggering. Dizziness became almost constant, and during the mornings there had been considerable blurring of vision.

Past history revealed that there had been a normal birth and early development. The only serious illnesses were scarlet fever at the age of 10 years, an apparently uncomplicated case of influenza in 1918, and attacks of what were described as "inflammatory rheumatism" in 1913 and 1926. The history by systems gave little additional data, except for constipation and a tendency toward early morning awakening. The personal history revealed that he had had a college education, and had been active in his duties as a minister. He was married, and had four children ranging in age from 7 to 16 years. The family history was negative.

Physical Examination. The physical examination revealed a well developed and nourished man, 5 feet 9¾ inches in height, weighing 143 pounds. There was a poverty of facial expression and a stooped posture. There was slight increase in moisture of the face. The mouth was edentulous. The nose, throat and respiratory tract were negative. The heart contour was normal, by percussion, and the heart sounds were regular and of good quality. The pulse rate was 90. The blood pressure was 148 mm. Hg systolic and 96 mm. diastolic in the supine position. Because the referring physician (Dr. Andrews) had found a low blood pressure, the patient was raised to a sitting position, and the blood pressure was found to be 68 mm. Hg systolic and 40 mm. diastolic. When standing, the patient complained of dizziness, and the blood pressure was found to be 44/?. The abdomen, genitalia and extremities were negative. A rectal examination revealed a marked relaxation of the anal sphincter; the prostate was normal.

Neurologic Examination. Cranial Nerves:

I. Normal.

II. Vision grossly normal. Fields were normal. Ophthalmoscopic examination showed normal discs. The retinal vessels were of normal caliber and distribution. There was no change in the retinal vessels noted with change in position.

III.) The pupils were of good size, equal, round and regular.
IV.) The reaction to light was perhaps somewhat sluggish. Extraocular move-
VI.) ments were normal.
V. Normal.
VII. Normal.
VIII. Normal.
IX.) Voice was husky. Examination of the larynx by Dr. W. A. Cassidy
X.) revealed no true paralysis, but a distinct lagging and loss of tone of the left vocal cord. Each ventricle appeared unusually deep and conspicuous.
XI. Normal.
XII. Normal.

Motor Status: No focal weakness or atrophy. Fine tremor of the extended fingers. There was no remarkable change in muscle tone, but there was a definite bradykinesia.

Coördination: Normal.

Reflex Status: Deep reflexes were equal and active. Superficial reflexes were normal, except for the abdominals which could not be obtained. No pathologic forms were present.

Sensory Status: Normal.

Sphincters: Rectal sphincter relaxed.

Laboratory Findings: Urinalysis negative. Hemoglobin 83 per cent. Red blood cells 4,130,000. White blood cells 6,200. Blood urea nitrogen 31 mg. per cent. Basal metabolic rate minus 2 per cent.

Lumbar Puncture: Pressure, 4 mm. of Hg. Cells 0. Protein normal. Wassermann reaction negative. Colloidal gold 1123332100.

Blood Pressure: During the period of hospitalization, there was no essential change in blood pressure until medication was given. Before placing the patient on medication, the effect of different drugs was tried.

	Prone	*Sitting*	*Standing*	
Blood pressure	108/70	84/58	58/40	Pulse 96.
0.5 c.c. of adrenalin (1–1000), given intramuscularly, and blood pressure after				
2 min.	188/94			
3 min.		258/158		
5 min.			154/96	(not dizzy)
7 min.	204/112			
10 min	194/106			
15 min.	158/98			
60 min.	140/90		64/58	(very dizzy)

The left hand was immersed in a pan of ice water, and very little change in blood pressure was noted.

	Prone	*Sitting*	*Standing*
Blood pressure	120/76	80/62	42/36
Ephedrine Sulphate, gr. 3/8, was given intramuscularly, and blood pressure after			
1 min.	140/96		
3 min.	148/110		
5 min.	158/106		
10 min.	160/116	104/84	50/38

Pilocarpine, gr. 1/6, given with a hot drink by mouth, produced only a moderate amount of perspiration and chiefly over the forehead, to a less extent in the axillae and not noticeably elsewhere.

Ergotamine tartrate orally produced no significant changes.

Reaction to Mecholin (Acetyl Beta Methylcholine Chloride):

	Prone	
Blood pressure	130/86	
Mecholin, .05 gm., given subcutaneously, and blood pressure after		
1 min.	52/10	Pulseless at wrist. Heart rate 36.
3 min.	58/32	Pulse— 68
6 min.	64/28	Pulse— 64
15 min.	68/28	Pulse— 84
30 min.	82/54	Pulse—112
45 min.	158/100	Pulse—112

Immediately after injection, the patient complained of a "dazed" sensation and of difficulty in breathing. The respirations increased to 32 per minute. There was also an immediate desire to void and a partial emptying of the bladder. Within a minute there was a profuse generalized perspiration, a great increase in salivation, and a sharp constricting feeling in the rectum.

Roentgen-Ray Findings: Roentgen-ray studies of the skull were normal.

Fluoroscopy of the chest showed the lungs and thorax to be essentially clear. The cardiac shadow was slightly, if at all, enlarged, regular in pulsation, and did not seem to change in size in the upright position during periods of faintness.

Cystoscopic Examination: A cystoscopic study was done by Dr. P. S. Adams, and the mucous membrane of the bladder appeared normal throughout. Cystometric studies showed evidence of an atonic, dilated bladder. There were 280 c.c. of residual urine with the cystometric examination. The first desire to void came after 300 c.c. had been introduced. The pressure was 0. Pain was experienced after 650 c.c. with a pressure of 4. Severe pain at 1100 c.c., with a pressure of 30. Strain elevated the pressure to 40.

Medication: During the hospital stay of 33 days, the patient was tried on benzedrine and ephedrine. Both drugs offered relief, although the benzedrine appeared to cause more discomfort in the way of palpitation and wakefulness. Because of the Parkinsonian features in this case, he was placed on stramonium, and this offered some relief. The best results were obtained with a combination of ephedrine, 3/8 gr. five times a day, and tincture of stramonium, minims 40, three times a day.

Comment

A review of the literature revealed few cases that exhibited the striking degree of sympathetic involvement reported in this case. From a neurologic standpoint, the patient presented a clinical picture of a Parkinsonian syndrome of the bradykinetic type. The posture was one of moderate flexion, the skin about the face oily, with a paucity of facial expression. There was no appreciable rigidity, but the movements of the extremities were very slow and apparently difficult to initiate. There was a fine tremor present which was not typical of basal ganglia disease.

The lack of sympathetic tone in this case was evidenced by the severe degree of postural hypotension, the impotency, the relaxed rectal sphincter and the dilated, atonic bladder. The response to drugs showed a marked improvement with adrenalin, and to a less extent with ephedrine. The reaction to acetyl beta methylcholine chloride, .05 gm., was particularly striking. The parasympathetic stimulation produced marked embarrassment with sharp decline in blood pressure in the prone position, a heart rate of 36 and inability to obtain the pulse at the wrist. It is of interest that the best results from the standpoint of treatment were obtained by a combination of ephedrine, a sympathetic stimulator, and stramonium, a parasympathetic inhibitor. It was felt that these two drugs exerted a synergistic effect.

Although other cases of postural hypotension fail to show the lack of sympathetic activity to the same degree, they do show, in association with other neurologic signs, some features of sympathetic embarrassment. In the course of the examination of neurologic patients two other cases of postural hypotension to a minor degree have been seen. A case of narcolepsy revealed a decrease in blood pressure from 126 mm. Hg systolic and 80 mm. diastolic to 112 mm. Hg systolic and 85 mm. diastolic in changing from the prone to the standing position. At the same time, the pulse rate increased from 72 to 100 per minute. A second case was a 59 year old farmer who complained of dizziness and faint spells associated with light-headedness. In addition, he had experienced difficulty in walking, especially at night, for two to three years previously. Blood pressure in the prone position was 110 mm. Hg systolic and 70 mm. diastolic, with a pulse rate of 72. On standing, the blood pressure dropped to 82 mm. Hg systolic and 65 mm. diastolic, and the pulse rate increased to 88. This patient had a diminution in vibratory sense in the lower extremities as the only neurological finding, and this was associated with an absence of free hydrochloric acid. Blood count, however, was normal. The neurologic features of this case were those of an early subacute combined sclerosis and associated postural hypotension. These findings are similar to those seen in the tabetic cases reported by Ellis and Haynes.[6]

It is doubtful that all cases of postural hypotension have the same etiology. It has been suggested that in some cases the carotid sinus may play a rôle, and others have suggested the possibility of a disturbance of the endocrine glands, toxic agents or trauma. In the case extensively reported in this paper, it is felt that the etiologic factor is a disorder of the nervous system, probably in the hypothalamic region, exerting depressing effect on the function of the sympathetic nervous system.

In view of the frequency of neurologic findings in cases of postural hypotension, a careful investigation of the neural status of each patient would seem to be indicated in an effort to determine the etiologic factor.

Summary and Conclusions

A review of the literature reveals that neurologic features are quite common in cases of postural hypotension. In recent years there has been an increasing interest in the possibility that postural hypotension is a manifestation of dysfunction of the sympathetic nervous system.

A case is reported which shows clinical features of a bradykinetic type of Parkinsonian syndrome associated with marked postural hypotension and other manifestations of sympathetic nervous system dysfunction.

As a result of pharmacological experience in this case, it is suggested that the best method of therapy is one which produces sympathetic stimulation with ephedrine or benzedrine, and parasympathetic inhibition by drugs of the atropine group.

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PRERENAL UREMIA DUE TO PAPILLOMA OF RECTUM*

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The term prerenal azotemia was adopted by Fishberg [1] in 1934 to designate that form of blood nitrogen retention not due primarily to renal insufficiency but to factors affecting the circulation or the composition of the blood before it reached the kidneys. The designation prerenal azotemia was deemed preferable to the older and frequently used expression extrarenal azotemia, since the latter failed to differentiate from the common azotemias due to obstruction of the urinary passages. Only in recent years, with the wide-spread development of laboratory medicine, has the commonplace character of prerenal types of nitrogen retention been recognized. Review of the literature, however, failed to reveal any example of high-grade prerenal azotemia due to non-obstructing rectal tumor. For this reason, the following case seemed worthy of mention.

Case Report

A. C. C. was a white male of 40 who was first seen at his home on March 26, 1939, at which time he complained of malaise and exhaustion. Five days previously he had gone to bed with headache, general aching, anorexia, weakness, stuffiness in the head, and feverishness. Three days later he felt worse, having nausea, increasing headache,

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and exhaustion. He also felt drowsy, but was unable to sleep. The only other feature elicited at that time was the fact that he had been getting up to urinate three or four times a night for several months or more. His past health had been quite good, and there had been no serious illnesses and no operations. The family history was non-contributory.

Physical examination revealed a well-nourished and developed middle-aged man who looked tired, but not acutely ill. There was considerable restlessness. Although he seemed rational, his responses were slow and at times a little uncertain. Respiration was just a bit labored. The complexion was sallow, but the conjunctivae were of good color. Temperature was 98° F., pulse was 80 per minute, and the blood pressure was 136 mm. Hg systolic and 96 mm. diastolic. The rest of the examination was negative, apart from a slightly enlarged liver. There was no dependent edema.

Examination of a specimen of urine disclosed a one plus albumin, innumerable granular casts, frequent white blood cells, and occasional red blood cells. Some type of nephritis with early uremia was suspected and hospitalization was advised, although not carried out until the following day.

By the time of admission to the Union Memorial Hospital the patient had become more drowsy and restless, and respirations were of the deep Kussmaul type. Emergency blood non-protein nitrogen was 101 mg./100 c.c. Urine was scant, with microscopic findings as before, specific gravity of 1.018, and gave a positive test for diacetic acid. The blood picture showed hemoconcentration and was as follows: red blood cells —6,120,000; hemoglobin—124 per cent; white blood cells—15,400, of which 80 per cent were polymorphonuclear cells. Sedimentation rate (corrected) was 12 mm. in one hour; volume packed red blood cells (Hematocrit)—59.

Although increased fluids by mouth and vein were begun at once, on the following morning the blood non-protein nitrogen was 120 mg., urea nitrogen 86 mg., creatinine 2.6 mg., sugar 129 mg., and chlorides 264 mg. Several times during the first night it was noticed that the patient appeared to be incontinent of a thin, watery material from the rectum. Rectal examination on the following day revealed a large, soft, sessile, overhanging mass, mostly posterior and easily palpated with the end of the examining finger. No areas of induration could be felt, although the mass bled easily and a colorless, thin, watery, mucoid secretion without fecal odor was expelled on removing the finger. Questioning revealed that it was to pass small quantities of this material that the patient had been getting up several times each night, urination being merely coincidental to these passages. Apparently, occasional similar passages had been occurring during the daytime in addition to a more formed stool daily.

Sigmoidoscopic examination by Dr. Harvey Stone confirmed the digital examination, and showed the mass to extend well up into the sigmoid colon beyond the reach of the instrument, although it could not be inserted full-length due to the poor cooperation of the patient. Again, 50 or 60 c.c. of the same non-fecal secretion were expelled through the sigmoidoscope. In view of the extremely low blood chlorides without a history of vomiting, it was decided to study the chloride content of this secretion. Qualitative test was strongly positive and quantitative analysis revealed 687 mg. of chloride per 100 c.c. This finding helped to clarify the clinical picture, it being assumed that the uremic-like syndrome, dehydration, and probable acidosis were due to the continued loss of electrolytes and fluid by way of the secretion from this massive tumor.

Therapy was first directed toward sufficient replacement of salt and fluids in the system to restore the normal electrolytic pattern and to supply the kidneys with water to carry off the excess nitrogenous wastes. Fluids and salt tablets by mouth, subpectoral infusions of normal saline, intravenous glucose and saline, and eventually a continuous intravenous cannula in the foot with alternating saline and glucose were all employed. During the first 24 hours in the hospital the clinical picture had pro-

gressed to the point of a toxic delirium and irrational state, with incontinence of the bowel and toxic paresis of the bladder, the latter necessitating catheterization several times daily. By this time, however, the kidneys had begun to function, and during the next four days the blood non-protein nitrogen dropped progressively to 92, 60, 36, and 26 mg./100 c.c., with corresponding increase in blood chlorides to 313, 346, 412,

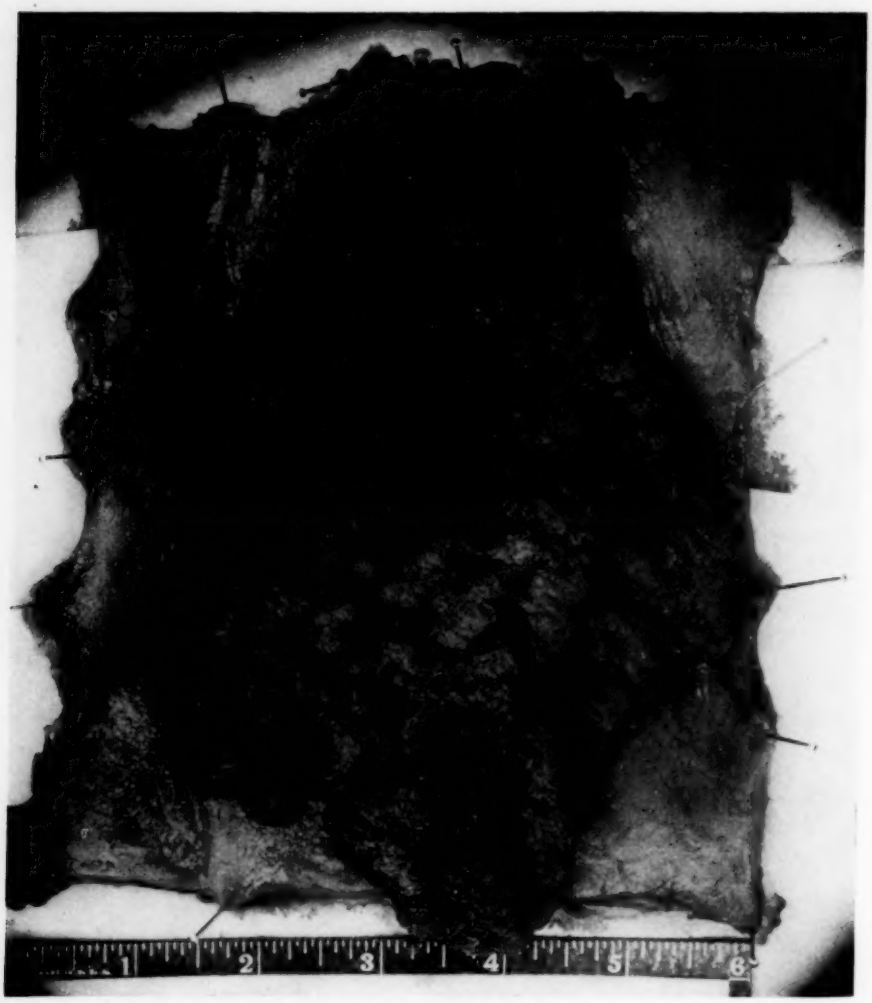

FIG. 1. Gross specimen of excised papilloma of the rectum.

and 644 mg. per cent respectively. Clinical improvement was even more striking, and the patient stated that he felt better than he had in months. The urine likewise gradually cleared, examination on the eleventh day after admission showing no albumin and only a rare white blood cell microscopically. Fifteen-minute phenolsulphonphthalein test at this time showed a dye excretion of 23 per cent, and a Fishberg concentration test revealed a maximum specific gravity of 1.022. Blood picture on the ninth hospital day was normal: hemoglobin 90 per cent; red blood cells 4,800,000, and white blood cells 6,700, with a normal differential count. Further studies of the

rectal secretion showed a chloride content of 726 mg./100 c.c. with total proteins of 1.0 gm. per cent, of which 0.4 gm. was albumin and 0.6 gm. globulin. Serum proteins were 5.8 gm., albumin 4.1 gm., globulin 1.7 gm., and A/G Ratio 2.4. Blood calcium was 9.0 mg. and blood phosphorus was 4.4 mg./100 c.c.

Roentgen-ray visualization of the kidneys disclosed them to be normal in size, shape and position with no evidence of urinary calculi. Barium enema revealed a large tumor mass, approximately six inches in length, extending from the lower sigmoid to the lower portion of the rectum.

On the sixteenth hospital day, the patient having continued well and having maintained normal blood non-protein nitrogen and chlorides, an abdomino-perineal resection of the rectal tumor was performed by Dr. Stone under cyclopropane anesthesia.

An unusually dilated, long Meckel's diverticulum was initially removed, following which the pelvic peritoneum was incised and the sigmoid freed as much as possible from its mesentery without too much interference with the blood supply. The sigmoid

FIG. 2. Section from papilloma of the rectum.

was then pushed down into the hollow of the sacrum and the pelvic peritoneum closed anteriorly. After routine abdominal closure, the patient was placed in the dorsolithotomy position and a perineal incision was made. The rectum, including the tumor and an inch of normal bowel on each end, was removed in toto, the external anal sphincter being preserved and the sigmoid being pulled down and sutured to the sphincter and surrounding structures. The patient left the operating room in good condition, 500 c.c. of citrated blood being given him during the latter part of the operation.

On gross pathological examination of the rectal specimen (figure 1), the tumor mass appeared approximately oval and measured 7″ long × 5″ wide × 1½″ thick. The villous, cauliflower-like growth had a uniform, soft consistency and was confined to the mucosa. Microscopic sections (figure 2) showed an extremely thick mucosa formed by bundles and coils of well-formed tubules side by side, with very little interstitial stroma. The cells were uniform in morphology and columnar in shape, with only occasional mitotic nuclei. There were many normal-appearing goblet cells. There was no invasion beyond the submucosa, although in several areas the tortuosity of the tubules and the buckling of the epithelial layers suggested a transitional stage which could be interpreted as early carcinoma. No lymphatic involvement was observed.

For the first week following operation the patient did fairly well, although obstinate distention accompanied by occasional vomiting and rather severe abdominal pain persisted in spite of continuous nasal-tube decompression, pitressin, and other customary measures. He began to have natural fluid bowel movements on the sixth postoperative day without, however, much relief of the distention and pain. Intravenous and subcutaneous fluids were maintained daily.

On the eleventh postoperative day the patient vomited 50 c.c. of bloody fluid, followed by a sharp drop in blood pressure and a state of surgical shock. Hematemeses of both bright red and dark blood of amounts varying from a few to several hundred cubic centimeters continued at frequent intervals until death ensued less than 72 hours later, on April 23. Both large and small transfusions of citrated blood, ample morphia sedation, intramuscular hemostatic material, and measures to combat shock were all unavailing. A few hours before death dark red blood was also passed per rectum.

Necropsy was performed by Dr. Walter C. Merkel. The following abstracts are from the report of the examination. Upon opening the abdomen, the intestines were found to be enormously distended and of a reddish-blue color. Many of the loops of intestines were stuck together by fibrinous adhesions. Slight pressure on the bowel revealed a perforation at the operative site where the diverticulum had been excised. There was a separation at one end of the suture line, with reënforcement on the serosa by an adjacent loop of ileum. The floor of the pelvis was intact, and the suture lines secure and actually healed. There was no exudate, and no evidence of metastasis.

Along the greater curvature of the stomach, in direct line of the esophagus, were many punched-out erosions, which averaged ½ to 2 cm. in diameter. Some of these ulcers extended down to the peritoneum. They were without inflammatory reaction and suggested to the pathologist a traumatic effect from the esophageal tube. The other pertinent findings were cloudy swelling of the liver and kidneys, acute splenic tumor, terminal right pleural effusion, and hematoperitoneum (thought to be postmortem due to manipulation of the intestinal tract). The kidneys definitely showed no signs of acute or chronic nephritis.

Comment

In the subject of this case report, there had been an excessive fluid and electrolyte loss from the bowel for at least several months, although the frequent small liquid passages were considered neither by the patient nor by the medical observers to be synonymous with a diarrhea. It appeared as if there occurred a collection of fluid material in the recto-sigmoidal region which stimulated a desire for passage when the amount reached a certain quantity. The passages were all small, at rather regular frequent intervals, and apparently in addition to a daily more formed stool. Sigmoidoscopic examination tended to confirm this impression, since the material extruded was a chloride-rich, thin, colorless, mucoid fluid without notable odor. It was considered by all observers to be a secretion from the large rectal mass (normal rectal mucosa cannot secrete salt) rather than a diarrheal stool from higher up in the intestinal tract. It was definitely established that the chloride content of this fluid was very high and almost double the correspondingly low blood chloride. Presumably, basic electrolyte was also lost in producing the clinical picture mentioned.

In association with the very evident dehydration and the probable acidosis, there was a clinical state simulating uremia. Very high blood non-protein nitrogen, albuminuria, and innumerable granular casts in the urine were accompanied by restlessness, headache, hyperpnea, irrational stupor, and incontinence of bowel and bladder. The extremely rapid disappearance of this clinical picture follow-

ing the parenteral administration of large quantities of water, salt and glucose, together with the equally rapid return of normal renal function and urinary findings, practically excluded all types of nephritis and primary kidney disease (a conclusion verified by autopsy). Consequently, this case was classified as an instance of prerenal uremia due to fluid and electrolyte loss per rectum, apparently by secretion from an essentially benign, non-obstructing, large rectal papilloma.

Brief mention should be made of the type of rectal tumor causing such a profound general disturbance. According to Rankin, Bergen, and Buie,[2] papilloma or villous tumor of the rectum is one of the rarest of benign intestinal tumors. Apparently originating from the intestinal mucosa in the crypts of Lieberkuhn, these tumors are usually sessile, vary considerably in size, have no tendency to invade the deeper structures, and microscopically show single or multiple layers of cylindrical cells supported by delicate vascular stroma. Bleeding, tenesmus, and frequent passages of large quantities of mucus are said to be common symptoms, although there is no characteristic syndrome. Although, both anatomically and clinically, villous papillomata have the nature of benign growths, approximately 20 per cent of all reported cases either were malignant when first observed or else became malignant subsequently. Since there is also a tendency to recur, radical extirpation is the operation of choice.

Finally, the immediate cause of death in the case reported is an unusual one and warrants notice. The patient died of gastric hemorrhages originating in a series of acute ulcers situated on the greater curvature in the direct line of the esophagus. This location and the absence of inflammatory reaction suggest mechanical erosions related in some way to the suction tube, although low tissue resistance due to the profound illness just preceding the operation may have been a contributing factor. It seems more likely that each of these erosions may have begun as a " fox-bite " type of lesion at the point of mucosal contact with an orifice in the nasal tube as a result of strong suction, rather than being due to the mere mechanical pressure or friction of the soft tube against the mucosa.

Discussion of Prerenal Azotemia

Blood nitrogen retention in the absence of kidney disease was recognized as long ago as 1832 when O'Shaughnessy [3] pointed to a rise of blood urea in cholera. However, modern interest in prerenal types of azotemia was first stimulated in 1914 by Tileston and Comfort,[4] who found pronounced elevations of blood non-protein nitrogen and urea in three cases of intestinal obstruction. In one patient who died, the blood non-protein nitrogen was 169 on the day before death and the clinical picture was described as strongly suggestive of uremia. Increased absorption of protein nitrogen from the intestine, concentration of blood through fluid loss by vomiting, profound shock, and possible intestinal toxin effect on renal function were suggested as etiological factors in the azotemia.

In 1923, Brown, Eusterman, Hartman, and Rowntree [5] called attention to the clinical picture of " duodenal toxemia," and ascribed it to a toxic nephritis, the renal injury being evidenced by degenerative lesions in the tubules and diminished phenolsulphonphthalein excretion. In 11 such cases of pyloric and duodenal obstruction, there ensued a state of intoxication simulating uremia, which was characterized clinically by nervous irritability, headache, flushed face, and dehydration, with incoherence, semi-consciousness, and tetany in extreme cases. Uri-

nalysis disclosed albumin, casts, red blood cells, and white blood cells, while blood examination revealed an increase in the urea and non-protein nitrogen content, lowering of plasma chlorides, increase in CO_2 combining power, and hemoconcentration. It is now known that complete obstruction of the alimentary canal at any point from the esophagus to the rectum will cause the concentration of non-protein nitrogen in the blood to rise, although it usually requires an obstruction at or above the duodenum to produce symptoms of uremic intoxication.

Similar findings have been described by various groups of investigators[6] working with experimental duodenal obstruction in dogs, the syndrome terminating in death within a few days unless prevented by parenteral salt solution.

The occurrence of prerenal azotemia in other digestive tract diseases may be briefly reviewed at this point. In addition to high intestinal obstruction, the condition which first stimulated interest in the non-renal types of nitrogen retention, azotemia of varying degrees may also follow the electrolyte and fluid loss from severe diarrhea,[3, 7] and more rarely from fistulae of duodenal, pancreatic, or jejunal origin.[8] However, simple elevation of the blood non-protein nitrogen rather than frank uremia appears to result from the dehydration, the electrolyte loss, the interference with protein absorption, and the increased destruction of nitrogen material in diarrheal diseases. The chloride loss in normal feces is insignificant, but the liquid stools excreted in diarrhea may contain large amounts of chloride, equivalent to as much as 15 gm. of sodium chloride per liter.[9] Likewise, there is an enormous rise in the output of sodium and potassium in extreme diarrhea.[9] Such loss may be sufficient to exceed the intake and, with the additional loss in the urine, cause a drain on the alkali stores of the body with accompanying dehydration.

There is more base than acid in all types of feces, so that severe diarrhea causes a withdrawal from the body fluids, and hence from the serum, of more base than acid radicles. Therefore, in addition to dehydration, some degree of acidosis (alkali deficit) usually occurs in pronounced diarrhea, unless there is vomiting, in which case the additional loss of chloride serves to equalize the acid-base deficit. In general, however, this type of azotemia is much more common in infants than in adults, apart from cholera in adults.

In the past few years, numerous reports have appeared concerning the association of marked azotemia with massive gastrointestinal hemorrhages.[10] The elevating effect of blood loss from any source on the level of the blood non-protein nitrogen had been studied many years ago by Taylor and Lewis,[11] and later by Buell.[12]

Other conditions related to the digestive tract which are on record as being accompanied by notable azotemia of extrarenal origin are various types of liver damage (especially the so-called "liver death" syndrome), acute pancreatitis and protracted vomiting from whatever cause (hyperemesis gravidarum, peritonitis, and postoperative vomiting).

To these are being constantly added many diseases unrelated to gastrointestinal pathology, such as traumatic and surgical shock, extensive burns, coronary thrombosis, congestive heart failure, reactions from intravenous transfusions and injections, diabetic coma, circulatory collapse of pneumonia and other infections, Addison's disease, heat cramps, serum disease, urticaria, and certain drug intoxications.

The clinical picture of prerenal azotemia [13, 14] is of necessity superimposed upon each of the widely diverse diseases mentioned above, although there are certain features common to all and certain characteristics differentiating the condition from azotemia due to organic kidney disease. As in patients with Bright's disease, azotemia may exist without clinical symptoms or be accompanied by fatigue and drowsiness, progressing into coma and associated with all of the classical features of uremia. In one of his latest papers,[14] Fishberg makes no differentiation between the character of the uremia of renal disease and that of prerenal azotemia, in that both exhibit a state of dehydration, demineralization, and retention of toxic waste products, and in that both have the same symptom-complex. Harrison and Morton [15] likewise state that the syndrome of prerenal azotemia simulates true uremia in both its chemical and clinical aspects. However, it is true that many of the late manifestations of chronic uremia, such as arterial hypertension, retinal changes, and uremic colitis and pericarditis, are uncommon in prerenal uremia, due to the acuteness and short duration of most of the causative mechanisms. In addition to the symptoms and signs of uremia, a variable degree of peripheral circulatory failure, manifested especially by collapsed peripheral veins with low venous pressure, will usually be detected if sought for carefully.

Laboratory studies are of essential importance in the diagnosis and management of prerenal uremia. The elevated blood non-protein nitrogen is due not only to a rise in urea, but also involves other fractions such as creatinine and uric acid. A marked rise in amino-acid nitrogen is of frequent occurrence in cases of advanced liver damage. Decrease in the blood chloride level is generally present, although there are exceptions. Corresponding reduction in the blood sodium is much more common than is realized, chiefly because this determination is not made routinely. There is recent evidence to indicate that, of the two, hyponatremia is more certain to produce dehydration and azotemia than hypochloremia, since the former leads to a diminished blood plasma volume irrespective of the fluid intake or loss. The acid-base equilibrium of the body, as indicated by the carbon dioxide combining power, may shift toward alkalosis or acidosis depending upon whether the chloride loss or the sodium loss is the greater. Hemoconcentration, as exhibited by increases in the total protein, erythrocyte count, hemoglobin and hematocrit value, is customarily found, and is useful in evaluating the degree of dehydration.

The important urinary features are (1) oliguria or anuria, (2) relatively high specific gravity which, however, may progressively decrease, and (3) the frequent appearance of albumin in small amounts, red blood cells and casts.

The striking clinical improvement and the rapid disappearance of the azotemia under intravenous saline and glucose administration present the final proof of the diagnosis. Such is the treatment indicated in the vast majority of cases of the prerenal syndrome.

The most problematic phase in the consideration of prerenal azotemia is its pathogenesis. Many theories have been advanced since the first recognition of this symptom-complex. Originally, diminished renal function [17] due to degenerative changes in the tubules, so-called "toxic nephritis," was thought to be the chief cause of the azotemia.[5] Then, with the demonstration of the life-saving qualities of fluid and salt [6, 8] and the rarity of demonstrable renal pathology in these cases, the condition was considered to be the direct result of dehydration

and electrolyte loss (particularly chlorides),[18] exaggerated in certain instances by increased destruction of protein and low arterial pressure. In pursuance of this concept, the term hypochloremic azotemia has been recently applied by numerous writers in a wide variety of conditions exhibiting azotemia of prerenal origin. In a comprehensive survey of the whole subject of extra-renal azotemia, Jeghers and Bakst [13] list six basic mechanisms, various combinations of which they believe will explain all of the many situations in which this syndrome arises. These interdependent and interrelated mechanisms are: (1) fall in blood pressure, (2) hypochloremia and hyponatremia, (3) dehydration, (4) increased protein catabolism, (5) loss of deaminizing power of the liver, and (6) local renal factors, including cases with tubular damage or edema of the kidney.

It remained for Fishberg [14] to give an unusually concise and well-formulated opinion as to the basic mechanism of prerenal azotemia. Briefly, he first defines the fundamental criterion of impairment of renal function as "a concentration of urine disproportionately low in comparison to urinary volume." He then considers the problem as to whether the azotemia is due to overloading of the kidneys (increased destruction of protein) or to failure of the kidneys, and concludes that the latter can be demonstrated as the cause if kidney function is judged in the light of the above definition. Besides citing previous evidence of impairment of renal function shown by urea clearance and other tests, Fishberg notes that in the vast majority of patients with prerenal azotemia, comparison of the specific gravity with the urinary volume shows a definite decrease in the concentrating ability. Thus, while a specific gravity of 1.020 is evidence of good kidney function when the urinary volume is normal, it is too low if the urinary volume is very small.

The mechanism of impairment of renal function is next discussed. It is shown that hypochloremia, low arterial pressure, toxic nephritis, and alkalosis cannot produce such impairment of themselves and that where present they appear to play accessory rôles at most. A strong array of evidence is finally presented to indicate that the primary pathogenetic factor in most, if not all, instances of prerenal azotemia is decrease in blood flow through the kidneys, mediated by peripheral circulatory failure with decrease in circulating blood volume. In this concept, the decreased urinary volume is ascribed to the diminished volume of blood flow through the glomeruli, and the lessened concentrating ability to impaired tubular function on an ischemic basis, with the intensity of the regressive changes in the tubular epithelium paralleling the degree of diminution in the renal blood flow.

The therapy of prerenal azotemia can be summed up in a few words. In addition to adequate treatment of the underlying disease process, the prime consideration is the restoration of the normal blood volume and electrolytic concentration. In almost all cases, this is best accomplished by the intravenous administration of sodium chloride solution with or without glucose. Peroral administration of fluid cannot be relied upon, and especially in the presence of vomiting, may be positively contraindicated. Relatively moderate amounts of glucose solution, given intravenously, may be sufficient to lessen protein destruction and to combat starvation acidosis, but large quantities of intravenous saline solutions are usually required. The total of both substances must be sufficient to restore the depleted fluid and electrolyte concentration in the body. This will automatically establish a normal urine output with rapid disappearance of the re-

tained nitrogen and other toxic products of catabolism. Furthermore, the kidneys, under fair working conditions, are sufficiently flexible in function to be capable of selective excretion of electrolytes of which there is an excess, and retention of those of which there is a deficiency. This obviates the need for separate administration of bicarbonate, lactate, or other special electrolytic solutions.

Blood and plasma transfusion are particularly indicated in the types of prerenal azotemia associated with shock, notably hemorrhage and trauma. There are other useful measures adaptable to specific cases, but these are of secondary importance and will not be discussed here.

Summary

1. An essentially benign, non-obstructing tumor of the rectum is added to the growing list of gastrointestinal and other miscellaneous conditions which have been observed to cause prerenal azotemia. The chief characteristics which helped to distinguish this instance of prerenal azotemia from the uremia secondary to organic renal disease were the absence of notable impairment of kidney function (especially high specific gravity), the laboratory evidence of marked dehydration (high hematocrit value, etc.) and of electrolyte deficiency, the discovery of the source of these losses from the body, and the quick reversibility of both subjective and objective findings upon fluid and salt restoration. Certain features in the clinical picture, such as normal fundi and normal blood pressure, were also of value in the differentiation. Autopsy verified the prerenal nature of these changes, for the kidneys showed no evidence of pathology apart from cloudy swelling. The mechanism in this case appeared to be one of progressive dehydration and electrolyte loss from the excessive secretion of the neoplasm, followed by sufficient oliguria to induce a clinical picture of acute uremia.

2. The whole subject of prerenal azotemia is briefly reviewed from the historical, clinical, pathogenetic, and therapeutic standpoints. The recent explanation of the pathogenesis by Fishberg appears to be the most logical, and at the same time, the most readily adaptable to all of the variegated types of prerenal azotemia. Under this concept, the azotemia is ascribed to impairment of renal function due to diminution in the volume of blood flow through the kidneys, which results in decreased urinary volume and urinary concentration. The diminished renal blood flow is in turn secondary to lessened circulating blood volume, i.e., peripheral circulatory failure.

3. Villous papilloma, a highly secretory type of rectal tumor, was present in this case. Rectal papillomata of the villous class are quite rare, which may help to explain the lack of similar case reports. Doubtless a corresponding prerenal uremia could follow other types of secretory rectal neoplasms, particularly should they be allowed to progress too long before medical attention is sought, as occurred in this case.

4. Massive hemorrhages from traumatic erosion ulcers of the stomach originating from a suction tube for distention appeared to be the immediate postoperative cause of death.

This patient was seen in consultation by Dr. Warfield T. Longcope and Dr. Harvey B. Stone, to whom the author is particularly indebted for suggestions in the management of this case. The author also wishes to express thanks to Dr. George W. Thorn for his help in the preparation of this report.

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EDITORIAL

THE SIGNIFICANCE OF HUMAN ATYPICAL ISOAGGLUTININS

THE discovery of the human blood groups and their routine determination in the selection of donors for transfusion removed the major peril of this procedure by eliminating most of the serious hemolytic reactions which followed the administration of incompatible blood. In spite of this precaution, however, an occasional reaction of this type has continued to occur. In a large majority of the cases reported in the earlier literature, it could be shown that errors in group determination had been made, and that the blood given had really been incompatible. Improvements in technic and adequate care in performing the tests can eliminate such errors, although they still occur if the tests are entrusted to inexperienced technicians.

In rare instances, reactions have followed the indiscriminate use of universal donors. As a rule, an individual belonging to Group O can serve as a donor for a patient belonging to any of the other groups, since the O cells introduced are not affected by the isoagglutinins which define the major groups. The plasma of O donors does contain agglutinins and probably other substances which can act on the cells of recipients of other groups, but usually this activity is abolished in the blood of the recipient, by dilution or possibly by direct neutralization so that no reaction occurs. In some cases, however, the active substances are present in the O serum in such high concentration that they are probably not adequately neutralized, and a reaction presumably may occur if such blood is given to a recipient of a different group. Such reactions can probably be avoided by measuring the activity of the serum of every prospective universal donor, using only those with a low agglutinin titer.

Apart from reactions of these types, however, serious hemolytic reactions may occur in patients who have received blood from a donor of the same blood group. In most cases this has occurred in patients who have received repeated transfusions, often from the same donor. Although well authenticated cases of this type are rare, a substantial number have now been reported. Among the most carefully studied instances of this type are three cases reported by Wiener and Peters.[1] Each received repeated transfusions from donors of the same group. After the earlier transfusions no clinical reaction occurred, although in some instances the expected rise in red cell count and hemoglobin was not obtained. The final transfusion in each case was followed by a severe hemolytic reaction. The usual cross matchings before the transfusions had shown no incompatibility. Blood serum taken from the patients after the last transfusion, however, when tested by a special

[1] WIENER, A. S., and PETERS, H. R.: Hemolytic reactions following transfusions of blood of the homologous group, with three cases in which the same agglutinogen was responsible, ANN. INT. MED., 1940, xiii, 2306–2322.

method, agglutinated the donor's cells. There was, therefore, an isoagglutinin concerned, which was different from the major group agglutinins, *a* and *b*.

A study of these sera showed that the agglutinin was identical with one which Landsteiner and Wiener [2] had demonstrated in rabbits which had received injections of red blood cells of rhesus monkeys. To the corresponding agglutinable factor, present in the monkey cells, they assigned the term *Rh*. A study of many human individuals showed that this same agglutinable factor is present in about 85 per cent of the cases. Landsteiner and Wiener [3] have studied the familial incidence of the *Rh* factor. It appears to be inherited as a Mendelian dominant character, independently of the *A*, *B*, *M* and *N* factors.

Except for the phenomenon of panagglutination, a human blood serum has never been found to contain agglutinin active on an agglutinable substance present in its own cells. In the remaining 15 per cent of individuals who lack the *Rh* factor, the injection of cells containing *Rh* may stimulate the production of the corresponding agglutinin. This obviously had occurred in these cases, and was associated with a severe reaction when such blood was reinjected.

It is probable that a similar mechanism constitutes the basis for many, at least, of these intra-group reactions, although in some cases it has been shown that the anomalous agglutinable factor is antigenically different from the *Rh* factor.

The number of *Rh*-negative patients who have received repeated transfusions of *Rh*-positive blood cells must be vastly greater than the number of clinical reactions which have been observed. There must be other factors necessary to bring about the formation of agglutinins and other antibodies in sufficient quantity to cause these reactions.

From the practical standpoint, this adds one more to the precautions necessary to ensure safety in transfusions. At present, reagents are not generally available for identification of the *Rh* factor in human blood, although Landsteiner and Wiener [3] have described a relatively simple method of preparing anti-*Rh* serum in guinea pigs. However, it may be possible by means of simple procedures to detect the existence of such incompatibilities. These agglutination reactions are quantitatively much feebler than those which determine the major blood groups, and, unlike them, are usually demonstrable only at low temperatures. If, therefore, the recipient and prospective donor have been shown by the usual tests to belong to the same major group, one may mix serum from the recipient and cells from the donor in a small tube, chill in ice water, centrifugalize, and resuspend the cells

[2] LANDSTEINER, K., and WIENER, A. S.: An agglutinable factor in human blood recognized by immune sera for rhesus blood, Proc. Soc. Exper. Biol. and Med., 1940, xliii, 223.

[3] LANDSTEINER, K., and WIENER, A. S.: Studies on an agglutinin (*Rh*) in human blood reacting with anti-rhesus sera and with human isoantibodies, Jr. Exper. Med., 1941, lxxvi, 309–319.

by shaking the tube gently. If clumps are present, the donor presumably is incompatible.[1] The reliability of this procedure, in either a positive or a negative sense, can be determined only by protracted trial. It is certain that reactions do not necessarily occur, even though the recipient's blood contains such agglutinins. Whether or not a negative preliminary test will suffice to exclude such reactions has not yet been demonstrated.

Intra-group reactions have also been described as occurring after a first transfusion, but only in women after labor, or after a still birth. Levine and Polayes[4] have recently reported such a case in the ANNALS OF INTERNAL MEDICINE. In these cases it is believed that the fetus has inherited from the father some agglutinable substance which was not present in the mother. She may then become "immunized" to this fetal factor, with the development of agglutinins, and react immediately if later transfused with blood containing it. The agglutinable factor in this case was not identical with the *Rh* factor of Landsteiner and Wiener. Such cases are relatively rare, and the immunization may depend upon placental defects which permit passage of fetal blood into the maternal circulation.

There is also evidence that such immunization of the mother may result in serious injury to the blood or tissues of the fetus. Levine et al.[5] have collected a number of cases in which repeated miscarriages or still births had occurred in women whose blood contained such "atypical" agglutinins. In a considerable proportion (seven of eleven) of the cases of erythroblastosis fetalis examined as to this point, the mother's blood contained atypical agglutinin—usually anti-*Rh* agglutinin.[4, 5] In several cases of erythroblastosis they showed that the mother's blood did not contain the *Rh* agglutinable factor, whereas it was present in that of the father and the affected children. Other agglutinable factors probably can cause similar disturbances, however, since in a few instances *Rh* was found in the mother's blood.

In most cases heterospecific pregnancies run a normal course, and the occurrence of erythroblastosis or fetal death presupposes some other contributory or predisposing factors. Further studies along these lines are manifestly needed, not only of these relatively rare congenital anemias, but of unexplained repeated miscarriages and still births.

P. W. C.

NOTICE TO READERS

Because of the unwieldy size of recent volumes of the ANNALS OF INTERNAL MEDICINE (approximately 2400 pages), it is planned hereafter to issue two volumes a year. The present volume (Vol. XV) will, therefore, terminate with the

[4] LEVINE, P., and POLAYES, S. H.: An atypical hemolysin in pregnancy, ANN. INT. MED., 1941, xiv, 1903–1908.

[5] LEVINE, P., KATZIN, E. M., and BURNHAM, L.: Immunization in pregnancy. Its possible bearing on the etiology of erythroblastosis fetalis, Jr. Am. Med. Assoc., 1941, cxvi, 825–827.

December issue, and the January issue will be Number 1 of Volume XVI. Each volume will have its own index.

Subscriptions will continue to be received on the annual basis.

It is hoped that this change will meet with the approval of our readers and will result in an added convenience in binding the volumes. A number of readers have already obtained binders for the ANNALS OF INTERNAL MEDICINE for the current volume, which, until this announcement, was expected to extend until June, 1942. These official binders have heretofore been manufactured in two books—one for the first six issues of the volume, and one for the second six issues. Those who have obtained the binders for the second six issues of the current volume may return the second binder to the Executive Offices at 4200 Pine Street, Philadelphia, Pa., and have the imprinting thereon corrected without charge, due to the change in the volume designation.

REVIEWS

Gastric and Duodenal Ulcers. By HAROLD AVERY, D.Sc., M.B., M.R.C.P. 110 pages; 14 × 22.5 cm. John Bale and Staples Ltd., 83–91 Great Titchfield St., London W1. 1940. Price, 7/6 d.

Because the pathology of uncomplicated peptic ulcer is usually so precise, the novice is apt to conclude that our knowledge of the entire subject is equally definite. Standard texts do little other than foster this view with their customarily didactic approach to the condition. The psychological aspect, and even the fundamental principles of dietary and medical therapy, are often buried in a maze of superficial rules and regulations.

The small volume herein reviewed succeeds in avoiding most of these pitfalls. The subject of peptic ulcer is discussed completely, starting with the basic anatomical and physiological features of the stomach and duodenum. Particular attention is given to etiology. The author in this section describes the constitutional type of individual so frequently affected with the condition. The chapter on treatment is quite complete, and there has been included a series of diets to be used during the different phases of the disease.

For a somewhat brief, but sound discussion of the subject of peptic ulcer this volume is recommended. It should be of considerable value to medical students and general practitioners.

F. G. D.

Obstetrics: Oxford Medical Outline Series. By HERVEY CLOCK WILLIAMSON, M.D., F.A.C.S., and GEORGE SCHAEFER, M.D. 113 pages; 14.5 × 22 cm. Oxford University Press, New York. 1941. Price, $2.00.

This attractive little book is the outline of obstetrics in the Oxford Medical Outline Series. The authors have accomplished their task of condensing what they consider the more important and practical considerations of obstetrics into an admirable outline. They state that they have purposely omitted historical data, illustrations and theories on debatable subjects. Important, recent advances such as those in chemotherapy and roentgen pelvimetry, however, have been included.

The book is arranged in a clear, easily followed outline form, with a blank page to be used for notes or drawings, opposite each page of text. There are 19 chapters. The bibliography is brief but embraces recent literature.

In the opinion of the reviewer, this book will find its chief usefulness among medical students who will welcome a brief, authoritative, well-organized and readily usable outline for review and reference.

J. E. S.

The Treatment of Diabetes Mellitus. 7th Edition. By ELLIOTT P. JOSLIN, A.M., M.D., Sc.D., HOWARD F. ROOT, M.D., PRISCILLA WHITE, M.D., and ALEXANDER MARBLE, M.D. 783 pages; 24 × 15.5 cm. Lea and Febiger, Philadelphia. 1941. Price, $7.50.

This is an outstanding book on diabetes, now appearing in its seventh edition. It has essentially the same authors contributing to this edition as in the sixth but here a larger part than ever has been borne by the associates of Dr. Joslin. The wide field of diabetes is here broken up into 30 chapters. This is practically the same division as in preceding editions except that a most interesting chapter on Allergy and Diabetes

has been added. The different chapters are thoroughly revised and rewritten. Approximately 100 pages have been added to the text.

Due note is given to the recent work of Young, Lukens and Best on the relation of the anterior lobe of the pituitary gland and diabetes.

The section on the treatment of diabetic coma (acidosis) should be read by all who are called upon to treat the diabetic. The authors feel that "experience has amply shown that alkalies are needless and if given in quantities necessary for effectiveness in a purely chemical sense, may be actually harmful." The authors are to be congratulated on maintaining their firm stand that the blood sugar be within normal limits and the urine be sugar free in the successfully treated diabetic.

Without question this classic, as in past editions, will remain essential to all who treat diabetic patients. It cannot be too highly recommended.

J. S. E.

Pulmonary Tuberculosis (A Synopsis). By JACOB SEGAL, M.D. 150 pages; 16 × 24 cm. Oxford University Press, New York, N. Y. 1939. Price, $2.75.

This small book is, as the title states, a synopsis of the fundamentals of pulmonary tuberculosis. The elementary, practical concepts of the pathogenesis, pathology, clinical types and treatment are presented clearly and in an interesting manner. The style is forceful without being dogmatic. There are a number of appropriate roentgen-ray illustrations.

The book is recommended to the medical student as an excellent introduction to the study of pulmonary tuberculosis. It should also be of help to health officers, social service workers and laymen interested in this subject. Unfortunately no references for collateral reading are given.

E. T. L.

COLLEGE NEWS NOTES

Gifts to the College Library

Acknowledgment is made of the receipt of the following reprints of publications by members of the College:

Dr. John E. Ashby (Associate), Dallas, Tex.—2 reprints;
Dr. Arthur John Atkinson (Associate), Chicago, Ill.—17 reprints;
Dr. Jacob M. Cahan, F.A.C.P., Philadelphia, Pa.—2 reprints;
Dr. Earle M. Chapman, F.A.C.P., Boston, Mass.—1 reprint;
Paul Richmond, Jr., F.A.C.P., Captain, (MC), U. S. Navy—2 reprints;
Dr. Leslie M. Smith, F.A.C.P., El Paso, Tex.—2 reprints;
Dr. Edward J. Stefanic (Associate), Lakewood, Ohio—2 reprints;
Dr. Alexander S. Wiener (Associate), Brooklyn, N. Y.—17 reprints.

Dr. Francis M. Pottenger, F.A.C.P., a former President and for many years a Regent of the College, founder and Director of the Pottenger Sanatorium, Monrovia, Calif., was honored on the occasion of his 72nd birthday, September 22, by an "Annual Home Coming" of friends and former patients at the Sanatorium. Approximately three hundred and fifty persons, most of them former patients, were present.

Dr. Robert H. Felix (Associate), Passed Assistant Surgeon of the United States Public Health Service, and for the past few years stationed at Lexington, Ky., as Chief of the Medical Service and Researcher in Drug Addiction at the United States Public Health Service Hospital, has been assigned to the Johns Hopkins University School of Hygiene and Public Health for the current academic year, where he will pursue postgraduate work leading to the degree of Master of Public Health.

Dr. William Harvey Perkins, Professor of Preventive Medicine at Tulane University Medical School, has been named Dean of Jefferson Medical College of Philadelphia. Dr. Perkins, who was graduated from Jefferson in the class of 1917, succeeds Dr. Henry K. Mohler, F.A.C.P., who died on May 16, 1941.

The New York Academy of Medicine began its sixteenth series of Friday afternoon lectures on October 31, 1941. All lectures are open to the medical profession and to medical students.

On the program appear the following papers by members of the College:

November 14, 1941—"Cancer of the Lung," Dr. J. Burns Amberson, Jr., F.A.C.P., Professor of Medicine, Columbia University College of Physicians and Surgeons;

January 23, 1942—"Plasma Proteins in Health and Disease," Dr. Robert F. Loeb, F.A.C.P., Professor of Medicine, Columbia University College of Physicians and Surgeons;

April 10, 1942—"Edema: Its Pathogenesis and Treatment," Dr. William Goldring, F.A.C.P., Associate Professor of Medicine, New York University College of Medicine.

Dr. Lyman Bruce Carruthers, F.A.C.P., who is Professor of Medicine and Dean of the Miraj Christian Medical School in Miraj, India, has been appointed Editor of the *Journal of the Christian Medical Association of India, Burma and Ceylon.*

Under the Presidency of Dr. Archibald A. Barron, F.A.C.P., Charlotte, the North Carolina Neurological and Psychiatric Association held a meeting at State Hospital, Morganton, Friday, October 24, 1941. Dr. Mark A. Griffin, F.A.C.P., and Dr. William R. Griffin, F.A.C.P., both of Asheville, discussed "Electro-Therapy."

Under the General Chairmanship of Dr. Walter L. Bierring, F.A.C.P., Iowa State Health Commissioner, Des Moines, the Iowa State Department of Health in cooperation with the Iowa State Medical Society sponsored a Special Institute on Industrial Health, September 22–24, 1941. One-day institutes were held in Council Bluffs, Waterloo and Dubuque.

Under the Presidency of Dr. Hyman I. Goldstein (Associate), Camden, the New Jersey Gastro-enterological Society will meet December 1, 1941, in Jersey City. The subject of this meeting will be "Surgical Problems in Benign Lesions of the Small Intestine and Malignant Lesions of the Large Bowel." Drs. Louis L. Perkel, F.A.C.P., Jersey City, Manfred Kraemer, F.A.C.P., Newark, Sigurd W. Johnsen, F.A.C.P., Passaic, and Hyman I. Goldstein (Associate) will participate in the discussion of the subject.

The Woman's Medical College of Pennsylvania held the opening exercises for its 92d Annual Session, September 17, 1941. The College has organized new Departments of Anesthesia, Gastro-enterology and Urology. Dr. Mary M. Spears, F.A.C.P., Professor of Gastro-enterology and Proctology, will head the Department of Gastro-enterology. New appointments to the faculty include Dr. E. J. G. Beardsley, F.A.C.P., Professor and Head of the Department of Medicine, and Dr. Mary H. Easby, F.A.C.P., and Dr. Clara L. Davis (Associate), Clinical Assistant Professors of Medicine.

The Mississippi Valley Medical Society held its 7th Annual Meeting in Cedar Rapids, Iowa, October 1–3, 1941. Among the Fellows of the College who participated in the program were:

Dr. J. Vardeman Bell, F.A.C.P., Kansas City, Mo.—"Sulfonamide Therapy";

Dr. Delon A. Williams, F.A.C.P., Kansas City, Mo.—"Gastric Lesions" and "Advances in Gastro-enterology";

Dr. LeRoy H. Sloan, F.A.C.P., Chicago, Ill.—"Clinico-Pathologic Conference";

Dr. Dan G. Stine, F.A.C.P., Columbia, Mo.—"The Evaluation of Cardiac Murmurs";

Dr. O. P. J. Falk, F.A.C.P., St. Louis, Mo.—"The Prevention of Coronary Disease."

The Dallas Southern Clinical Society held the second series of its program of courses for the Continuation of Medical Study in Dallas, October 27–29, 1941. Courses were offered in Cardiology, Diabetes, Diagnostic and Medical Gynecology, Traumatic Surgery, Pediatrics—Respiratory Diseases, Dermatology and Syphilology, Roentgenology—Procedures and Interpretation, and Urology. Among those who conducted these courses were:

Dr. Henry M. Winans, F.A.C.P.—"Hemodynamics of the Circulation," "Hypoglycemic States and Hyper-insulinism" and "Diagnosis and Treatment of Cardiac Arrhythmias";

Dr. W. Grady Reddick, F.A.C.P.—"Roentgen Aid in the Diagnosis of Heart Disease" and "Insulin Shock and Coma";

Dr. William H. Potts, Jr., F.A.C.P.—"Circulatory Function Tests" and "Pre- and Post-Operative Care of the Diabetic";

Dr. Robert M. Barton, F.A.C.P.—"Principles of Electrocardiography. Practical Application of Electrocardiography. Tracings and Patients" and "Coronary and Peripheral Vascular Diseases";

Dr. Merritt B. Whitten (Associate)—"Principles of Electrocardiography. Practical Applications of Electrocardiography. Tracings and Patients";

Dr. David W. Carter, Jr., F.A.C.P.—"History, Etiology and Incidence of Diabetes Mellitus," "Heart Failure: Edema, Dyspnea, Cyanosis" and "The Treatment of Cardiac Failure";

Dr. J. Shirley Sweeney, F.A.C.P.—"Pathological Physiology of Diabetes Mellitus";

Dr. T. Haynes Harvill (Associate)—"Determination of the Diabetic Diet" and "Computation and Preparation of the Diabetic Diet";

Dr. M. Hill Metz, F.A.C.P.—"The Insulins";

Dr. William H. Bradford (Associate)—"Congenital Abnormalities of the Respiratory Tract";

Dr. H. Leslie Moore, F.A.C.P.—"The Tonsil and Adenoid Problem";

Dr. Everett C. Fox, F.A.C.P.—"Early Syphilis: Diagnosis, Treatment, Drugs, Reactions," "Dermatological Therapeutics," "Demonstration and Discussion of Cases of Common Skin Diseases" and "Demonstration of Bed Patients with Various Types of Skin Diseases, Differential Diagnosis, Treatment, Prognosis and Discussion";

Dr. John E. Ashby (Associate)—"Congenital Syphilis";

Dr. J. Bedford Shelmire, F.A.C.P.—"Eczema: Diagnosis and Treatment," "Demonstration and Discussion of Cases of Common Skin Diseases" and "Dermatitis from Plants";

Dr. J. Harvey Black, F.A.C.P.—"Allergic Diseases of the Respiratory Tract";

Dr. John G. Young, F.A.C.P.—"Tuberculosis in Childhood."

Dr. Joseph I. Linde, F.A.C.P., New Haven, has been appointed City Health Officer for a six-year term by Governor Hurley of Connecticut.

Dr. William deB. MacNider, F.A.C.P., Kenan Research Professor of Pharmacology of the University of North Carolina School of Medicine, Chapel Hill, recently delivered three lectures on "Acquired Resistance of Tissue Cells," under the auspices of the Department of Materia Medica and Therapeutics of the University of Michigan Medical School, Ann Arbor. The subjects of Dr. MacNider's lectures were: "Repair of Tissue and Tissue Resistance," "The Aging Process and Tissue Resistance" and "The Adjustability of the Life Process to Injurious Agents."

Dr. Walter Baumgarten, F.A.C.P., St. Louis, has been elected Secretary of the Missouri State Medical Association.

The American Roentgen Ray Society held its 42nd Annual Meeting in Cincinnati, Ohio, September 23–26, 1941. Among the speakers were:

Dr. Tom D. Spies, F.A.C.P., Cincinnati, Ohio—"The Manifestations of Vitamin Deficiencies as They Affect the Practice of Roentgenologists";

Dr. Byrl R. Kirklin, F.A.C.P., Rochester, Minn.—"The Meniscus Sign-Complex: A Pathognomonic Index of Early Ulcerating Cancer of the Stomach";

Dr. Harold J. Stewart, F.A.C.P., New York, N. Y.—"Contributions of Roentgenology to the Diagnosis of Chronic Constrictive Pericarditis."

Dr. Raymond Hussey, F.A.C.P., Baltimore, Md., spoke on "The State Medical Society's Responsibility in Mental Hygiene" and Dr. John E. Gordon, F.A.C.P., Boston, Mass., spoke on "Epidemiologic Observations in War-Time London," at the 70th Annual Meeting of the American Public Health Association held in Atlantic City, N. J., October 11–17, 1941.

During September Dr. Horton R. Casparis, F.A.C.P., Professor of Pediatrics at Vanderbilt University School of Medicine, Nashville, Tenn., gave a series of lectures on pediatrics in Oakland and San Diego, and conducted a course of lectures and clinical discussions before the Southwestern Pediatric Society in Los Angeles, Calif.

The Medical Society of Delaware held its 52d Annual Session at Wilmington, October 7–8, 1941. Among the speakers at this meeting were:

Dr. Harold W. Jones, F.A.C.P., Philadelphia, Pa.—"Discussion of the Transfusion of Whole Blood, Plasma and Serum";

Dr. Lawrence J. Rigney, F.A.C.P., Wilmington, Del.—"Analysis of the Clinical Data of 47 Proved Cases of Carcinoma of the Pancreas."

A series of extramural courses for physicians was held at Hurley Hospital, Detroit, under the auspices of the Michigan State Medical Society and the University of Michigan Medical School. Among those who conducted the courses were:

October 1, Dr. John M. Sheldon (Associate), Ann Arbor—"Office Management of the Allergic Patient";

October 8, Dr. Douglas Donald, F.A.C.P., Detroit—"Medical Complications of Pregnancy";

October 15, Dr. Richard M. McKean, F.A.C.P., Detroit—"Office Management of the Diabetic Patient."

Recently Dr. Philip I. Nash, F.A.C.P., Brooklyn, N. Y., was honored at a testimonial dinner in recognition of his activities in the Coney Island community. Dr. Nash has been chairman of the Medical Board of Coney Island Hospital and of the Harbor Hospital for many years, has been President of the Medical Society of the County of Kings and was on the faculty of the Long Island College of Medicine.

A course of postgraduate lectures on Geriatrics to be given at Marquette University School of Medicine in November has been announced by the Medical Society of Milwaukee County. Among those who will conduct this course are:

Dr. George Morris Piersol, F.A.C.P., Philadelphia, Pa.—"The Problem of Aging from the Internist's Angle";

Dr. Hans H. Reese, F.A.C.P., Madison, Wis.—"The Central Nervous System in the Aged."

The American Academy of Ophthalmology and Otolaryngology held its 46th Annual Meeting in Chicago, Ill., October 19–23, 1941. Dr. Burt R. Shurly, F.A.C.P., Chairman of the Academy's Preparedness Committee, spoke on "The Rôle of the Academy in National Defense" and Dr. Louis H. Bauer, F.A.C.P., Hempstead, N. Y., spoke on "Aviation Medicine."

Dr. Julius Lane Wilson, F.A.C.P., New Orleans, has been appointed President of the Tuberculosis and Public Health Association of Louisiana to fill the unexpired term of Dr. William H. Perkins, who resigned to become Dean of Jefferson Medical College of Philadelphia.

Among the speakers at the annual symposium of Duke University School of Medicine and Duke Hospital on "Problems of Civil and Military Emergencies," held at Durham, N. C., October 16–17, 1941, were:

Dr. Thomas T. Mackie, F.A.C.P., New York, N. Y.—"Problems in Nutrition During Periods of Crisis and Food Shortage";

Dr. Alvan L. Barach, F.A.C.P., New York, N. Y.—"Clinical Use of Oxygen";

Dr. Russell L. Cecil, F.A.C.P., New York, N. Y.—"Treatment of Influenza and Respiratory Epidemics."

Dr. John B. Youmans, F.A.C.P., Nashville, Tenn., spoke on "Observation on Nutrition in France," November 5, 1941, at a meeting of the College of Physicians of Philadelphia. On December 3, 1941, Dr. Walter L. Palmer, F.A.C.P., Chicago, Ill., will address the College on the "Rôle of Acid Gastric Juice in Gastric and Duodenal Ulceration," and on January 7, 1942, Dr. John H. Musser, F.A.C.P., New Orleans, La., will speak on "The Heart That Is Aging."

Dr. Tom D. Spies, F.A.C.P., Associate Professor of Medicine, University of Cincinnati College of Medicine, and Col. W. Lee Hart, F.A.C.P., Surgeon of the 8th Corps Area, Fort Sam Houston, Tex., were among the guest speakers at the Tarrant County Medical and Surgical Clinics held in Forth Worth, Tex., October 8, 1941.

The Association of American Medical Colleges held its 52nd Annual Meeting in Richmond, Va., October 27–29, 1941. Among the speakers were:

George F. Lull, F.A.C.P., Colonel, (MC), U. S. Army—"The Place of the Medical Colleges in the National Defense Program";

Dr. Alvan L. Barach, F.A.C.P., New York, N. Y.—"Physiological Problems Involved in Aviation Medicine."

Among the speakers at the 24th Annual Meeting of the American Dietetic Association held in St. Louis, Mo., October 20–23, 1941, were:

Dr. Russell M. Wilder, F.A.C.P., Rochester, Minn.—"Nutrition and National Defense";

Dr. Seale Harris, Sr., F.A.C.P., Birmingham, Ala.—"Recent Investigations in Pellagra";

Dr. Leon Schiff, F.A.C.P., Cincinnati, Ohio—"Use of Meulengracht Diet in the Treatment of Peptic Ulcer";

Dr. Harry L. Alexander, F.A.C.P., St. Louis, Mo.—"Allergy";

Dr. John B. Youmans, F.A.C.P., Nashville, Tenn.—"Observations of Health Conditions in Relation to the Food Supply and State of Nutrition of Groups in France and Spain."

The 58th Annual Meeting of the American Clinical and Climatological Association was held at Skytop, Pa., October 16–18, 1941. Among the speakers at this meeting were:

Dr. C. Sidney Burwell, F.A.C.P., Boston, Mass.—"Relation of Some Physical Signs to Alterations in the Circulation Produced by Congenital Heart Disease";

Dr. A. Carlton Ernstene, F.A.C.P., Cleveland, Ohio—"Angina Pectoris in Young Individuals with Aortic Insufficiency";

Dr. William S. McCann, F.A.C.P., Rochester, N. Y.—"Use of Concentrated Plasma Protein Solutions in Congestive Heart Failure";

Dr. Francis M. Rackemann, F.A.C.P., Boston, Mass.—"Intrinsic Asthma";

Dr. Lay Martin, F.A.C.P., Baltimore, Md.—"Studies on Regional Enteritis and Some Other Conditions Causing Prolonged Partial Obstruction of the Small Intestine."

The Aero Medical Association of the United States held its 13th Annual Meeting in Boston, Mass., October 31–November 2, 1941. Speakers at this meeting included:

Dr. Jan H. Tillisch (Associate), Rochester, Minn.—"The Physical Maintenance of Transport Pilots";

Irving Ershler (Associate), Lieutenant, (MRC), U. S. Army—"Circulatory Responses to Anoxia in Man."

John R. Poppen, F.A.C.P., Commander, (MC), U. S. Navy, was installed as President of the Association at this meeting.

Dr. John A. Toomey, F.A.C.P., Cleveland, Ohio, spoke on "Diagnosis of Poliomyelitis" and Dr. Archibald L. Hoyne, F.A.C.P., Chicago, Ill., spoke on "Principles of Treatment of the Acute Stage of Poliomyelitis" at a symposium on poliomyelitis conducted by the Chicago Medical Society on October 15, 1941.

Dr. Walter F. Donaldson, F.A.C.P., Secretary of the Medical Society of the State of Pennsylvania, Pittsburgh, was recently cited to receive one of the Merit Awards of Northwestern University. The citation on the award reads "In recognition of worthy achievement which has reflected credit upon Northwestern University and each of her alumni."

Dr. Elliston Farrell (Associate) has been appointed Assistant Professor of Tropical Medicine at Tulane University of Louisiana School of Medicine at New Orleans. Formerly, Dr. Farrell was Assistant Clinical Professor of Medicine at Long Island College of Medicine, Brooklyn.

The New England Postgraduate Assembly, sponsored by the state medical societies of Massachusetts, New Hampshire, Rhode Island, Maine, Vermont and Connecticut, was held at Harvard University, October 29–30, 1941. Dr. J. Burns Amberson, Jr., F.A.C.P., Professor of Medicine, Columbia University College of Physicians and Surgeons, New York, and Dr. George W. Thorn, F.A.C.P., Associate Professor of Medicine, Johns Hopkins University School of Medicine, Baltimore, were among the speakers at this meeting.

Dr. Harold M. Coon, F.A.C.P., Statesan, Wis., has been appointed Superintendent of the Wisconsin General Hospital and the Wisconsin Orthopedic Hospital for Children, Professor of Hospital Administration and Executive Secretary of the University of Wisconsin Medical School, Madison, succeeding Dr. Robin C. Buerki, who was recently appointed Dean of the University of Pennsylvania Graduate School of Medicine and Director of Hospitals of the University of Pennsylvania, Philadelphia.

On October 14, 1941, Dr. Charles R. Castlen, F.A.C.P., Glendale, Calif., spoke on "Present Day Concepts of Tuberculosis in Pregnancy" at a joint meeting of the Los Angeles Obstetrical and Gynecological Society and the Trudeau Society of Los Angeles.

Dr. Francis J. Braceland, F.A.C.P., Dean of Loyola University School of Medicine, Chicago, participated in a symposium on "Current Trends in Neuropsychiatry" at the University of Illinois College of Medicine, October 11, 1941.

Harry G. Armstrong, F.A.C.P., Major, (MC), U. S. Army, will deliver the Gehrmann Lectures for 1941–42 of the University of Illinois College of Medicine. On October 21 and 22 Major Armstrong lectured on "Medicine in Aviation," "Selection and Care of Fliers" and "Effects of Flight on Man."

On October 3, 1941, Major Henry M. Thomas, Jr., F.A.C.P., Chief of the Medical Section, Station Hospital, Fort George G. Meade, Md., addressed the Baltimore City Medical Society on "The Health of Selectees in Training," and Dr. Robert H. Riley, F.A.C.P., State Health Director, Baltimore, Md., spoke on "Public Health Aspects of Selective Service."

The meeting of the New York Academy of Medicine on October 2, 1941, was devoted to the memory of the late Sir Frederick G. Banting, F.A.C.P. A memorial and scientific address on "Prevention of Diabetes from the Experimental Viewpoint" was given by Dr. Charles H. Best, who succeeded Dr. Banting as Director of the Department of Physiology and the Banting and Best Department of Medical Research at the University of Toronto Faculty of Medicine. At this meeting Dr. Elliott P. Joslin, F.A.C.P., Boston, Mass., spoke on "The Use of Insulin in Its Various Forms in the Treatment of Diabetes."

Dr. Jean A. Curran, F.A.C.P., Dean of Long Island College of Medicine, Brooklyn, has been appointed Acting President of the College, succeeding Dr. Frank L. Babbott, who resigned.

Among the speakers at the 52nd Annual Meeting of the Association of Life Insurance Medical Directors of America, held in New York, N. Y., October 23–24, 1941, were:

Dr. Burrill B. Crohn, F.A.C.P., New York, N. Y.—"Achlorhydria and Its Ultimate Significance";

Dr. Edgar V. Allen, F.A.C.P., Rochester, Minn.—"Peripheral Arterial Diseases";

Dr. Edward S. Dillon, F.A.C.P., Philadelphia, Pa.—"Recent Developments in Diabetes."

The American Association of the History of Medicine held its semi-annual meeting at the University of Kansas Medical School, Kansas City, October 24–25, 1941, under the auspices of the Quivira Medical History Club of Western Missouri and Kansas. Among the speakers at this meeting were:

Dr. Bert F. Keltz, F.A.C.P., Oklahoma City, Okla.—"Indian Medicine in the Southwest";

Dr. Thor J. Jager (Associate), Wichita, Kan.—"Bibliographic Notes on Claude Bernard";

Dr. William S. Middleton, F.A.C.P., Madison, Wis.—"Medicine at Valley Forge";

Dr. Richard M. Burke (Associate), Clinton, Okla.—"Significant Dates in the History of Tuberculosis."

Dr. Logan Clendening, F.A.C.P., Kansas City, Mo., presented an exhibit of early American medical journals, and Dr. Edward H. Hashinger, F.A.C.P., Kansas City, Mo., an exhibit of early nursing bottles and pap dishes.

Dr. Christopher C. Shaw, F.A.C.P., Bellows Falls, Vt., has been on active duty as Lieutenant Commander in the Medical Corps of the U. S. Naval Reserve, assigned to the Naval Air Station, Pensacola, Fla. On September 30, 1941, he was graduated from the School of Aviation Medicine and immediately thereafter appointed an Instructor in Cardiology on the faculty of the School.

Dr. Joseph H. Barach addressed the Ohio County Medical Society at Wheeling, W. Va., on October 10, 1941. His subject was: "Treatment of Diabetes Since the Advent of Insulin." On October 14, he addressed the Elk County Medical Society at St. Marys, Pa., on "Treatment of Diabetes by the General Practitioner of Medicine." On October 15, 1941, Dr. Barach addressed the Crawford County Medical Society at Meadville, Pa., on the subject "Diabetes as a Scientifically Treated Disease."

Civil Service Commission Seeking Nurses for Service in Panama Canal Zone

The Civil Service Commission has announced a special examination to recruit nurses for work in the Panama Canal. No written test will be given, and applications will be accepted at the Commission's Washington office until further public notice.

The entrance salary is $168.75 a month with provision for promotions at stated intervals. Appointments will be made to general staff duty and psychiatric work.

Applicants must not have passed their thirty-fifth birthday. Further information and application forms may be obtained from the Commission's representative in any first- or second-class post office or from the central office in Washington, D. C.

OBITUARIES

DR. WARREN HORACE FAIRBANKS

Dr. Warren Horace Fairbanks was born in Newark, Vt., on February 28, 1884. He received his early education in St. Johnsbury, Vt., and then prepared for the Methodist ministry at Boston University. After spending several years as pastor of a church in Philadelphia, he decided to study medicine, and was graduated at the age of thirty-two from New York Homeopathic Medical College and Flower Hospital. Dr. Fairbanks then interned at the Ann May Memorial Hospital, Spring Lake, N. J., 1916–17, and in the succeeding years, having developed an interest in chest diseases, took postgraduate courses at the Trudeau School of Tuberculosis and at Colorado Springs. Upon returning to practice at Freehold, N. J., in 1926, he was made Attending Physician to the Tuberculosis Preventorium at Farmingdale, N. J., and its Medical Director in 1937, a position which he has held ever since. At the time of his death he was also Medical Director of Allenwood Sanitarium and Monmouth County Hospital for Tuberculosis, and Attending Phthisiologist to the Fitkin Memorial Hospital. His medical societies included the New Jersey State Society, the American Medical Association, the National Tuberculosis Association and the National Sanitarium Association. He was a Past President of the Monmouth County Medical Society, and had been a Fellow of the American College of Physicians since 1931.

Dr. Fairbanks took a deep interest in the affairs of his community and was widely known as a public speaker. He collected antiques, and was especially interested in American pewter. When more leisurely days came they were apt to be given over to fishing or shooting.

Dr. Fairbanks suffered a cerebral hemorrhage and died August 5, 1941, at the age of fifty-seven.

GEORGE H. LATHROPE, M.D., F.A.C.P.,
Governor for New Jersey

DR. AUSTIN B. JONES

Dr. Austin B. Jones was born in Shackelford, Mo., October 1, 1891. He died at his home in Kansas City, Mo., September 3, 1941.

Dr. Jones attended the Missouri Valley College, Marshall, Mo., and later entered the St. Louis University School of Medicine, where he received his M.D. degree in 1915. He served one year's internship at the City Hospital, St. Louis, and then returned to Shackelford, where he practiced until 1919, when he located in Kansas City, Mo.

Dr. Jones was a Diplomate of the American Board of Internal Medicine, a member of the Jackson County Medical Society, Missouri State Medical Society, the American Medical Association, and had been a Fellow of the American College of Physicians since 1928.

Dr. Jones, familiarly known to all his devoted friends as "A. B.," was a real student, a hard worker and an honest, straightforward physician. He was absolutely ethical and would not associate with a physician that was unethical. The medical profession, as well as Kansas City, has lost a very capable physician and a grand fellow.

A. C. GRIFFITH, M.D., F.A.C.P.,
Governor for the State of Missouri

DR. MARION LEE COMPTON

Dr. Marion Lee Compton, F.A.C.P., of the Veterans Administration Facility at Augusta, Ga., died of heart disease March 27, 1941. The appearance of his obituary in this journal has been unintentionally delayed by failure of the local College officer to submit it for publication.

Dr. Compton was born at Forth Worth, Tex., August 19, 1894. He received his medical training at the University of Texas School of Medicine, graduating in 1917, thereafter pursuing postgraduate study in psychiatry and neurology at St. Elizabeth's Hospital, Washington, D. C. Dr. Compton was the Medical Officer at the Veterans Bureau at Dallas, Tex., 1919–1923; at Little Rock, Ark., 1924–1931; and at Lyons, N. J., 1931–1934. He became Clinical Director of the Veterans Administration Facility at Lexington, Ky., 1934–35, Medical Supervisor, Neuropsychiatric Service, U. S. Veterans Administration, 1935–39, and then Manager of the Veterans Administration Facility at Augusta from 1939 to the time of his death. During the World War he served as a First Lieutenant in the Medical Corps of the U. S. Army at Camp Travis, Tex. He was a member of the American Psychiatric Association and had been a Fellow of the American College of Physicians since 1935.

DR. GEORGE KINGSLEY OLMSTED

Dr. George Kingsley Olmsted, F.A.C.P., of Denver, Colo., died June 25, 1941, of coronary thrombosis and diabetes mellitus. He was born in Chicago, Ill., October 16, 1871; attended Oberlin College, 1890–92; received his Ph.B. from Colorado College in 1894, his Ph.D. from Yale University in 1898, and his M.D. degree from Denver and Gross College of Medicine in 1903.

For many years Dr. Olmsted was on the faculty of the Denver and Gross College of Medicine and the University of Colorado School of Medicine. He was a Lieutenant Colonel (Retired) in the Medical Reserve Corps of the U. S. Army, and a member of the staff of the Denver General, St. Luke's, and Physicians and Surgeons Hospitals; a member of the Denver Medical Club, City and County Medical Society of Denver, Colorado State Medical Society, Colorado Tuberculosis Association, formerly President of the Colorado State Board of Health, and had been a Fellow of the American College of Physicians since 1924.

DR. RALEIGH WILLIAM BAIRD

Dr. Raleigh William Baird, F.A.C.P., of Dallas, Tex., died July 13, 1941. He was born in Shreveport, La., in 1870, received his A.B. degree from Southwestern University in 1893, and his M.D. degree from Bellevue Hospital Medical College, New York City, in 1896. He interned at the Bellevue Hospital for a period of two years.

For many years Dr. Baird was Visiting Physician to the Baylor University Hospital and Chief of the Medical Department of the Dallas Medical and Surgical Clinic Hospital. He was a member of his county and state medical societies, the Southern Medical Association, Fellow of the American Medical Association, and had been a Fellow of the American College of Physicians since 1921.

1942 PROGRAM OF INTENSIVE POSTGRADUATE COURSES ARRANGED BY THE AMERICAN COLLEGE OF PHYSICIANS

THE Advisory Committee on Postgraduate Courses, with the approval of the Committee on Educational Policy and the Executive Committee of the College, announces the following courses, arranged through the generous coöperation of the directors and the institutions at which the courses will be given.

This is the fifth year of this activity by the College. The courses are organized especially for Fellows and Associates of the College, but where facilities are available, courses will be open to those with adequate preliminary training who are now preparing either to meet the requirements of membership in the College or certification by the American Board of Internal Medicine.

The courses are made available by the College to its members at minimum cost, because the College assumes full responsibility for promotion, advertising, printing and registration. The College continues its program of giving courses in mid-winter in addition to those arranged immediately preceding its Annual Session in April. Eventually the program may be extended to include courses at other seasons of the year also, if the demand for such courses justifies such extension.

Fees.—The registration fee, regardless of the institution or course selected, is based on $20.00 for each week. One-half of the total registration fee for any course shall be paid at time of registration, and the balance shall be paid not later than one week in advance of the opening of any course. The advance payment may be refunded by the College to any registrant who for adequate reason is unable to pursue the course, provided notice of withdrawal is registered ten days in advance of the opening of the course. Checks should be drawn to the order of "W. D. Stroud, Treasurer," and mailed to E. R. Loveland, Executive Secretary, American College of Physicians, 4200 Pine Street, Philadelphia, Pa. All tuition fees received by the College are transferred in bulk sum to the institution or director and faculty of each course.

Registration.—Inasmuch as this is a general announcement of the courses without the detailed outlines of courses and the lists of officers of instruction, the more complete and final bulletin for each course will be issued at a somewhat later date. An official registration form will accompany that bulletin. Registrations will be accepted in order of receipt. The maximal registration indicated for each course must be strictly adhered to.

The College will record all registrations with the respective institutions offering courses. A matriculation card will be sent to each registrant when his fee has been paid in full.

COURSE NO. 1—ALLERGY
(February 2–14, 1942)

The Roosevelt Hospital, Department of Allergy,
New York, N. Y.

ROBERT A. COOKE, M.D., F.A.C.P., *Director*
(Minimal Registration, 6; Maximal Registration, 8)

Fee, $40.00

This course essentially will be a repetition of the courses given under the auspices of the College by Dr. Cooke in 1940 and 1941. It will be devoted to the practical and theoretical aspects of allergy. There will be clinics, conferences, laboratory work and demonstrations. Such conditions as asthma, perennial and seasonal (hay fever) coryza, urticaria, angioedema, eczema, dermatitis, gastrointestinal and cerebral allergies, vernal catarrh and periarteritis nodosa will be presented and studied in the clinic and laboratory. Practical work will consist of history taking, physical examinations, skin testing—direct and by passive transfer, and various laboratory procedures. The laboratory will take up preparation of allergens, Dale reactions, bacterial and mold cultures, preparation of autogenous vaccines, vital capacity studies, etc.

Registrants may obtain their lunches at the hospital.

COURSE NO. 2—THE DIAGNOSIS AND TREATMENT OF HEART DISEASE
(February 2–14, 1942)

Massachusetts General Hospital and the House of the Good Samaritan,
Boston, Mass.

PAUL D. WHITE, M.D., F.A.C.P., *Director*
(Minimal Registration, 20; Maximal Registration, 30)

Fee, $40.00

The course will cover the fundamentals in the diagnosis and treatment of disorders of the heart and circulation. Approximately half of the time will be devoted to demonstrations and small group instruction in pathology, electrocardiography, roentgenology, and the study of heart sounds and murmurs in the clinics and wards of the Massachusetts General Hospital and at the House of the Good Samaritan. The remainder of the time will be devoted to clinics and clinical-pathological discussions of special phases of heart disease and its treatment, conducted by members of the Massachusetts General Hospital staff and by members of other hospital staffs in Boston particularly qualified to discuss their subjects.

COURSE NO. 3—GENERAL MEDICINE
(February 2–14, 1942)

University of California Medical School and Stanford University School of Medicine, San Francisco, Calif.

WILLIAM J. KERR, M.D., F.A.C.P., *Director*
STACY R. METTIER, M.D., F.A.C.P., *Associate Director*
University of California Medical School

ARTHUR L. BLOOMFIELD, M.D., F.A.C.P., *Director*
DWIGHT L. WILBUR, M.D., F.A.C.P., *Associate Director*
Stanford University School of Medicine

(Minimal Registration, 20; Maximal Registration, not limited)

Fee, $40.00

This course is designed to give a survey of the recent developments in all phases of general medicine. Related topics will be presented in the form of symposia. The lectures and discussions will be supported by clinics, ward demonstrations and clinical, pathologic and radiologic conferences. Emphasis will be placed on some of the newer drugs, such as the sulfonamide preparations, and on endocrine products. Round table discussions will include diseases of the gastrointestinal tract, the cardiovascular system and the respiratory tract. Attention will be given to new aspects of nutrition and of psychosomatic relationships in medicine. There will be a symposium on new diagnostic procedures as well as on the treatment of diseases of the blood.

The meetings will be held at the University of California Hospital, the Stanford University Hospitals and the San Francisco Hospital.

COURSE NO. 4—INTERNAL MEDICINE
(February 2–14, 1942)

Johns Hopkins University School of Medicine and University of Maryland School of Medicine, Baltimore, Md.

WARFIELD T. LONGCOPE, M.D., F.A.C.P., *Director*
GEORGE W. THORN, M.D., F.A.C.P., *Associate Director*
Johns Hopkins University School of Medicine

MAURICE C. PINCOFFS, M.D., F.A.C.P., *Director*
H. RAYMOND PETERS, M.D., F.A.C.P., *Associate Director*
University of Maryland School of Medicine

(Minimal Registration, 20; Maximal Registration, 50)

Fee, $40.00

The Johns Hopkins University School of Medicine in collaboration with the University of Maryland School of Medicine will offer a Postgraduate Course of Instruction in Chemotherapy, Hematology, Nutrition and Endocrinology. Each of the subjects will be allotted approximately one-fourth of the total available time.

Instruction in Chemotherapy will consist of a systematic review of the chemotherapy of bacterial infections which will be presented in six three-hour sessions. This review will cover the following subjects: pharmacology of the sulfonamide drugs, their mode of action, methods of administration, toxicology; the rôle of immunity in response to chemotherapy; sulfonamide therapy in pneumonia, streptococcal infections, meningitis, gonococcal infections, urinary tract infections, bacillary dysentery, staphylococcal infections, etc. The subject matter will be presented in a series of lectures and clinics supplemented by round table discussion.

Instruction in Hematology will include a systematic survey of the field with particular emphasis on recent developments. An essential feature of the course will be provision for individual study of the blood of representative hematological diseases with a discussion of interpretation, diagnosis and treatment. *Physicians will be required to provide their own microscopes.*

A session will be devoted to transfusions of blood, of plasma and of blood substitutes. Problems connected with reactions to transfusions will be discussed. The administration of blood banks will be considered.

Instruction in Nutrition will be concerned primarily with a discussion of recent advances in our knowledge of the metabolism of minerals and vitamins. Mineral and vitamin deficiencies will be considered in lectures and demonstrations under the following headings: physiological importance, clinical manifestations of deficiency, methods of detection and treatment.

Instruction in Endocrinology will include studies of the chemical nature and physiological action of the various hormones. Clinical manifestations

of disturbances in adrenal, gonadal, pancreatic, parathyroid, pituitary and thyroid functions will be illustrated in clinics and discussed at round table conferences. The relative efficacy of specific hormone preparations will be considered. Particular attention will be directed to a discussion of tests which have proved their usefulness in the differential diagnosis of endocrine disorders. It will be possible for small groups of physicians to participate in the daily ward visits on the Clinical Metabolic Unit of the Johns Hopkins Hospital.

At the Johns Hopkins University School of Medicine the instruction will be supervised not only by Drs. Longcope and Thorn, Director and Associate Director of the course, but also by Drs. M. M. Wintrobe, Associate in Medicine, and W. Barry Wood, Associate in Medicine.

COURSE NO. 5—GASTROINTESTINAL DISEASES

(February 2–7, 1942)

Graduate Hospital, University of Pennsylvania,
Philadelphia, Pa.

HENRY L. BOCKUS, M.D., F.A.C.P., *Director*

(Minimal Registration, 20; Maximal Registration, 48)

Fee, $20.00

Faculty: Thirty members of the Faculty of the Graduate and Undergraduate Schools of Medicine of the University of Pennsylvania.

A number of symposia have been arranged in order to emphasize recent advances in the diagnosis and treatment of various digestive tract disorders. These symposia include:

(1) Value of Liver Function Tests in Diagnosis and Treatment;
(2) Diagnosis of Chronic Gastritis;
(3) Colonic Disorders;
(4) Diseases of the Esophagus;
(5) The Relationship of Nutritional Deficiency to Alimentary Tract Disease;
(6) Functional Diseases of the Digestive Tract;
(7) Regional Enteritis and Enterocolitis;
(8) Pancreatic Disorders;
(9) Peptic Ulcer;
(10) Achlorhydria.

The course includes six hours of practical demonstrations of gastroscopy, sigmoidoscopy, bile microscopy, intestinal parasites, coprology and liver function tests. Several periods of ward round demonstrations of interesting cases and of clinical pathological conferences are included in the schedule.

Time: 8:30 a.m. to 5:30 p.m., Monday to Friday inclusive. Saturday, 9:00 a.m. to 1:00 p.m.

COURSE NO. 6—ALLERGY

(April 6–18, 1942)

Washington University School of Medicine and
Barnes Hospital, St. Louis, Mo.

HARRY L. ALEXANDER, M.D., F.A.C.P., *Director*

(Minimal Registration, 6; Maximal Registration, 8)

Fee, $40.00

The purpose of this course is to review intensively the subject of clinical allergy in both its theoretic and practical aspects. Informal lectures, clinics, demonstrations and examination of patients will be devoted to the study of asthma, hay fever, allergic rhinitis, urticaria, eczemas, gastrointestinal and other manifestations of allergy.

Laboratory procedures will include demonstrations and practice of the preparation of allergens and autogenous vaccines, skin testing, cytologic examination of sputum and nasal secretion and vital capacity determinations.

Practical work on assigned cases will consist of history taking, physical examination, skin testing, examination of secretions, and other relevant laboratory work.

COURSE NO. 7—ARTHRITIS AND RHEUMATIC DISEASES

(April 13–18, 1942)

The Mayo Foundation, University of Minnesota, and
The Mayo Clinic, Rochester, Minn.

PHILIP S. HENCH, M.D., F.A.C.P., *Director*

(Minimal Registration, 20; Maximal Registration, 35)

Fee, $20.00

This course will cover the diagnosis and treatment of the commoner diseases of muscles and joints, including muscular rheumatism, rheumatoid arthritis and osteo-arthritis. Special emphasis will be placed on the treatment of gonorrheal arthritis by the sulfonamides, the treatment of rheumatoid arthritis by gold salts, the diagnosis and treatment of gout, the treatment of suppurative arthritis and war wounds of joints.

Members of the staff of The Mayo Clinic and invited guest speakers will conduct the course under the supervision of Dr. Philip S. Hench and Dr. Charles H. Slocumb, of the service for rheumatic diseases at The Mayo Clinic.

COURSE NO. 8—PERIPHERAL VASCULAR DISEASES, INCLUDING HYPERTENSION

(April 6–18, 1942)

The Mayo Foundation, University of Minnesota, and
The Mayo Clinic, Rochester, Minn.

EDGAR V. ALLEN, M.D., F.A.C.P., *Director*

(Minimal Registration, 35; Maximal Registration, 100)

Fee, $40.00

This course will include a discussion of the physiology of the peripheral circulation, the syndrome of hypersensitive carotid sinus, occlusion of the inferior and superior vena cava, temperature of the skin as a measure of peripheral circulation, consideration of nail fold capillaries, venous pressure, venography and infra-red photography, erythromelalgia, colorimetry, symptoms of peripheral vascular disease, cervical rib and scalenus syndrome, graphic and audible recording of arterial murmurs, studies on the speed of arterial circulation, thromboangiitis obliterans, terminology and examination in peripheral vascular diseases, periarteritis nodosa and " vascular allergy," arteriosclerosis obliterans, aneurysm and arteriovenous fistula, sudden arterial occlusion, diseases of minute blood vessels, temporal arteritis and cold allergy, glomus tumor, varicose veins, phlebitis and other diseases of the veins, methods of investigation in peripheral vascular diseases and their clinical value, critical consideration of some methods of treatment of peripheral vascular diseases, differential diagnosis in edema of the extremities, lymphedema, pulmonary hypertension, systemic hypertension, the retinae in hypertension, normal blood pressure and its physiologic variations, prediction of the development of hypertension, classification of essential hypertension, hypertension and pregnancy, paroxysmal hypertension, arterioles in hypertension, treatment of hypertension, orthostatic tachycardia and hypotension, renal insufficiency in hypertension, the electrocardiogram in hypertension, congestive heart failure due to hypertension, experimental hypertension, history and results of treatment of hypertension with kidney extract, occupation and vascular diseases, shock, arteriosclerosis and other conditions.

Instruction will be furnished by thirty-five physiologists, surgeons, internists and pathologists, including several nationally recognized guest speakers. Formal presentations, conferences and clinics will be given.

COURSE NO. 9—GASTROINTESTINAL DISEASES

(April 6–18, 1942)

University of Chicago, The School of Medicine,
Billings Hospital, Chicago, Ill.

WALTER L. PALMER, M.D., F.A.C.P., *Director*

(Minimal Registration, 30; Maximal Registration, 75)

Fee, $40.00

The purpose of this course is to review the field of Gastro-enterology with particular reference to the etiology, pathogenesis, diagnosis and treatment of the diseases of the digestive tract. The program will consist chiefly of lectures and discussions given by authorities in the various subjects. Ample opportunity for discussion will be allowed and encouraged.

Lectures will be given in Room M–137 of the Department of Medicine at the University of Chicago, Billings Hospital. Registrants should report to this room when the course opens.

COURSE NO. 10—INTERNAL MEDICINE

(April 6–18, 1942)

University of Minnesota Medical School, Minneapolis, Minn.

CECIL J. WATSON, M.D., F.A.C.P., *Director*

(Minimal Registration, 30; Maximal Registration, 50)

Fee, $40.00

The continuation course in Internal Medicine will be given at the Center for Continuation Study, University of Minnesota. It will be of interest to members of the American College of Physicians, qualified physicians who plan to apply for admission to the College, prospective candidates for the American Board of Internal Medicine and such other physicians who limit their practice mainly to Internal Medicine and are eligible for admission under the regulations.

The course will be presented in seven sections: cardiovascular diseases, hematology, metabolism and endocrinology, infectious diseases, diseases of the gastrointestinal tract, pulmonary diseases and deficiency states. The teaching program will consist of lectures, movies, clinics, demonstrations and round table question and answer discussion periods. Mimeographed outlines of lectures and demonstrations will be supplied without extra charge. Unless otherwise specified all classes will be held in the Center for Continuation Study. Bus transportation will be furnished to all off-campus clinics and demonstrations. A faculty of over forty teachers is being assembled

from the graduate school staff in Minneapolis and St. Paul and The Mayo Foundation. In addition, distinguished teachers from other centers will take part. Each part of the course will be presented by men who have given special attention to that sub-division of the subject.

The group will live in the Center for Continuation Study where pleasant, comfortable rooms and good meal service are available. Rooms are from $6.25 to $8.75 a week. Meals are $1.75 a day. Parking in the Center for Continuation Study garage is $.50 a day. There will be a luncheon each day at which members of the faculty will conduct discussion periods. Tea will be served at four o'clock. Medical movies will be shown in the lounge after dinner. The registrants will be able to make full use of the medical library facilities of the general library of the University of Minnesota, which is located just a short distance from the Center for Continuation Study. Recreation periods will be held on Wednesday and Saturday afternoons.

The course will start at 9:00 a.m., April 6, and close at 2:00 p.m., April 18, 1942. A certificate of attendance will be issued by the University of Minnesota to all who attend the prescribed number of exercises.

COURSE NO. 11—TUBERCULOSIS

(April 13–18, 1942)

University of Colorado School of Medicine and Hospitals, Denver, Colo.

JAMES J. WARING, M.D., F.A.C.P., *Director*

(Minimal Registration, 10; Maximal Registration, 25)

Fee, $20.00

The purpose of this course is to review the most important clinical features of all stages of pulmonary tuberculosis. Complications of tuberculosis, especially tracheo-bronchial tuberculosis and tuberculous effusions, with and without pneumothorax, will be presented for discussion. Demonstrations will be given of the tuberculin reaction and laboratory methods of diagnosis by animal inoculation and culture of the tubercle bacillus. The class will have the opportunity daily to examine many patients with minimal, moderately advanced and far advanced tuberculosis, many patients with silicosis, patients suitable for varied forms of collapse therapy, patients after phrenic operation, patients taking artificial pneumothorax, patients being treated by the Monaldi method for closure of cavity, patients after thoracoplasty, after lobectomy and after pneumonectomy. Conferences centered around roentgen-ray films will be held daily.

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THE CLINICAL SYMPTOMS AND SIGNS OF VITAMIN B COMPLEX DEFICIENCY *

By WILLIAM H. SEBRELL,† M.D., F.A.C.P., *Bethesda, Maryland*

THE symptoms caused by deficiencies in various members of the vitamin B complex probably constitute our greatest medical problem in the deficiency field. There are eight known substances which may be called members of the vitamin B complex. These are thiamin, riboflavin, nicotinic acid, pyridoxine, pantothenic acid, p-aminobenzoic acid, choline and inositol. At least four of these appear to be needed by man. These are thiamin, riboflavin, nicotinic acid and pyridoxine. Deficiencies in the remaining known members of the B complex have been shown to cause various symptoms in experimental animals.

It has been shown that a deficiency in pantothenic acid causes a graying of the hair in black rats, and Daft and Sebrell [1] have found that a hemorrhagic necrosis of the adrenal glands in rats is caused by a deficiency in pantothenic acid. Further observations on patients are necessary to determine whether or not this substance is needed by man.

A deficiency in choline causes a fatty liver, and it appears quite likely that this also may be a human essential.

It has been reported that a deficiency in inositol causes a loss of hair in mice, and Ansbacher [2] has very recently reported that a deficiency in p-aminobenzoic acid causes graying of hair in black rats. The possible clinical importance of deficiencies in these substances remains to be determined. In addition, these eight substances probably do not represent the entire vitamin B complex. Evidence based on animal experimentation indicates that other unidentified substances probably are present.

* Read at the Boston meeting of the American College of Physicians, April 23, 1941.
† Chief, Division of Chemotherapy, National Institute of Health, U. S. Public Health Service, Bethesda, Maryland.

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Spies, Bean and Ashe [3] have furnished us with clinical evidence on human pyridoxine deficiency. They report symptoms of weakness and difficulty in walking which they were able to correlate with a low excretion of pyridoxine and which improved under treatment with pyridoxine. Spies, Hightower and Hubbard [4] and Jolliffe [5] also have independently reported that pyridoxine is beneficial in controlling some of the symptoms of paralysis agitans although it cannot be regarded as a specific for this disease. We have treated approximately 30 very old and severe cases of paralysis agitans with large doses of pyridoxine without any apparent benefit. It appears to be definitely indicated that in early cases of paralysis agitans it should be given thorough trial.

There is a wealth of clinical data on the symptomatology of thiamin, nicotinic acid and riboflavin deficiency. Sydenstricker has discussed the symptoms of multiple deficiencies which are so commonly seen in the clinic.

All of you are familiar with the gross symptoms of extreme thiamin deficiency such as enlargement of the heart, extreme edema, tenderness of the calf muscles, weakness, hyperesthesia and neuritis which characterize beri beri. It is the less extreme forms with which we are particularly concerned in the United States. Soma Weiss and Wilkins [6] and Dustin, Weyler and Roberts [7] have directed special attention to heart changes. Goodhart and Jolliffe [8, 9] have called attention to the peripheral neuritis occurring as a complication of alcoholism, and other diseases in which there is interference with thiamin intake or utilization. More recently the experimental work of Williams, Mason, Wilder and Smith [10] has directed attention to a group of symptoms hitherto undescribed in early thiamin deficiency. Their observations, made under controlled conditions, have shown that the early symptoms of thiamin deficiency may be undue anxiety, weakness, lack of interest and a group of mental symptoms which would ordinarily be diagnosed as neurosis. The possible significance of thiamin deficiency in conditions such as these is of the greatest clinical importance, especially since all of the dietary data available to us indicate that thiamin-deficient diets are very prevalent in our population. The best opinion now is that normal adults require about 1.8 milligrams of thiamin a day.

The symptoms of nicotinic acid deficiency as characterized by the typical lesions of pellagra are also quite familiar. The dermatitis which may be bullous, resembling in many ways the early stages of a severe sunburn, appears most frequently either on exposed surfaces or in regions subject to irritation. However, there are many cases of nicotinic acid deficiency which have minimal skin lesions or no skin lesions at all. These cases most frequently show loss of weight, weakness, mental depression, and gastrointestinal upset with indigestion and sometimes diarrhea. There is usually a reduction or absence of hydrochloric acid in the stomach. In the stomatitis which also is frequently found in these cases the tongue is usually red and there may be extensive ulceration; the buccal lesions usually swarm with

organisms of the Vincent's type which may lead to an incorrect diagnosis of Vincent's angina as reported by King.[11] The patients usually complain of a burning or scalded sensation in the mouth. In addition to this type of the disease, Cleckley, Sydenstricker and Geeslin [12] and Jolliffe, Bowman, Rosenblum and Fein [13] have independently described an acute mental manifestation of nicotinic acid deficiency in which no skin lesions are seen. These patients are either chronic alcoholics or old people in whom there is a severe mental disturbance similar in many respects to cerebral arteriosclerosis. They show delirium, an extreme mental confusion, and disorientation. They may have sucking reflexes and cog wheel rigidities. These cases are thought to represent an acute nicotinic acid deficiency and seem to require large doses of nicotinic acid intravenously, following which they rapidly return to normal, where formerly the death rate was extremely high. The normal adult requirement for nicotinic acid is probably about 18 milligrams daily.

The symptoms of human riboflavin deficiency were not recognized as a separate entity until late in 1938.[4] Since then several reports have appeared indicating that the condition is rather common. The typical lesion is a macerated linear fissure in each angle of the mouth similar to a lesion which earlier had been called an angular stomatitis. However, the entire lip is also involved. The lips become scaly, appear to be chapped, and are shiny, reddened and denuded in appearance, especially along the line of closure. For this reason the entire lip lesion has been designated cheilosis. In many cases we also have seen a superficially eroded lesion located just inside the nares. A fissure may also occur in this area at the mucocutaneous junction. The tongue takes on a red or slightly purplish color and can be distinguished from the bright red tongue of pellagra. Many cases have a seborrheic dermatitis of varying extent which may be exceedingly mild, involving only the fold around the nares or the eyes. These lesions consist of small greasy scales on a slightly erythematous base. In some instances the ears and other folds of the body are involved.

Some observers have found cases in which there were hard seborrheic plugs across the bridge of the nose which have been designated as "shark skin." It was noted by Spies and his associates [15] that many cases had eye symptoms such as photophobia and lacrimation, with reddening of the conjunctiva. Bessey and Wolbach [16] found vascularization of the cornea to be the earliest and most important manifestation of riboflavin deficiency in the rat, and Eckardt and Johnson [17] have reported a high incidence of keratitis in rats on riboflavin deficient diets. In retrospect it appears that the lesions of riboflavin deficiency were confused with pellagra in the older literature and were diagnosed as pellagra *sine pellagra*. There are many references in the older literature to eye lesions accompanying pellagra. The very early writers on pellagra, such as Soler [18] (1791) and Rampoldi [19] (1795), refer to such eye symptoms as inflammation of the cornea, corneal ulcers, and opacities. Photophobia, mydriasis, conjunctivitis, pain, failing

vision, and superficial inflammation of the cornea have been described by other writers on pellagra. It seems not unlikely now that in view of the close association frequently seen between riboflavin deficiency and pellagra, many of these lesions may have been due to riboflavin deficiency. Spies, Vilter and Ashe [20] have called attention to such lesions and stated that more than 70 per cent of the patients in their nutrition clinic with frequent recurrences of pellagra, beri beri, or riboflavin deficiencies, also have visual disturbances. Spies, Bean and Ashe [15] noted that these disturbances disappeared in from four to six days following the administration of riboflavin. Following the demonstration by animal experimentation that keratitis was a manifestation of riboflavin deficiency in the rat, and the clinical demonstration by Spies and his associates that certain eye symptoms clear up on the administration of riboflavin, Kruse, Sydenstricker, Sebrell and Cleckley [21] demonstrated that 47 patients with symptoms of photophobia, dimness of vision, burning sensation and circumcorneal injection, mydriasis, and iritis showed slit lamp evidence of a vascularizing keratitis. In these patients, there was spectacular improvement following the administration daily of 5 to 15 milligrams of riboflavin. Also, repeated slit lamp examination showed rapid resolution of the keratitis and emptying of the vessels in the cornea.

Johnson and Eckardt [22] have also demonstrated that riboflavin is of value in the treatment of rosacea keratitis. It therefore appears that keratitis is definitely a part of the syndrome caused by riboflavin deficiency.

Sebrell, Butler, Wooley and Isbell [23] have recently reported an extensive study on riboflavin balance. These studies indicate that there is very rapid decrease in the urinary excretion of riboflavin following a decreased intake in the diet. They also show that the human riboflavin requirement is approximately 3 milligrams per day for an adult woman. This quantity of riboflavin can be obtained from a liberal diet. In the treatment of riboflavin deficiency I would recommend the use of not less than 6 milligrams per day and up to 15 milligrams. Some cases seem to respond rather slowly to therapy. It is not to be supposed that all cases having fissures at the angles of the mouth are due to riboflavin deficiency. Pollack [24] has recently seen such cases due to ill fitting dentures, bearing no relation to riboflavin deficiency.

There is evidence to indicate that the above deficiency diseases are of the utmost clinical importance in the United States and Dr. Wilder has already discussed the nutrition program which is designed to help prevent these deficiencies. Dietary survey data show that there are large numbers of people living on diets which do not contain enough thiamin, nicotinic acid, or riboflavin to meet what we consider to be adequate levels of intake. This is probably reflected in an enormous number of cases with mild symptoms of each of these deficiency diseases, and it is exceedingly difficult to make an estimate of the total number. However, from the number of patients appearing

in the clinics, where special efforts are being made to recognize these conditions and the number of patients showing vague symptoms of the above types which improve on treatment with these vitamins, it is not unlikely that these deficiencies constitute one of our largest medical problems. From the point of view of preventive medicine, the evidence is conclusive that there is a great opportunity to improve the health of the nation by increasing the vitamin B complex content of the diets of a considerable part of our population.

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SCARLET FEVER IMMUNIZATION *

By JOHN A. TOOMEY, M.D., F.A.C.P., *Cleveland, Ohio*

THERE is need for a procedure that will actively immunize susceptibles against scarlet fever. Such immunization is necessary for the personnel of contagious disease hospitals, preventoriums and orphan asylums; it is no less necessary for the young if the complications of scarlet fever are to be avoided. However, the need may not seem apparent when it is noted that for the past 40 years scarlet fever has been increasing in morbidity, but decreasing in mortality.[1] On the other hand, everyone will admit that the severity or mildness of the infection has no bearing on the degree or type of complication which may occur.

The Dicks have described an immunizing toxin, the efficacy of which has been tested under the most adverse circumstances, i.e., among groups of nurses working in contagious disease hospitals. In such institutions, Hektoen and Johnson [2] reported a morbidity rate of 7.7 per cent; Place,[3] as high as 8.6 per cent; Benson and Rankin,[4] a variable rate, from 4 to 10 per cent; Anderson and Reinhardt,[5] 12.8 per cent in known positive Dick test reactors. On an average, 12 per cent of the student nurses in this training school (City Hospital, Cleveland) have contracted scarlet fever. In 1922, the attack rate was as high as 17.7 per cent.

Over 6,000 nurses have been admitted to the School of Nursing, City Hospital, Cleveland, during the past 20 years. Out of such a group, it could be expected that at least 480 might contract scarlet fever. If one considers that five dollars a day is a minimal charge for hospital care and that the scarlet fever patient is hospitalized for 30 days, it would cost the institution about $72,000.00 to care for such a number of cases. Not only the cost, but inconvenience to the hospital and the time lost by nurses are items of administration which have to be considered.

Since early 1925, immunization has been offered to all of our susceptible nurses. An immunization record of each student was kept. This included a record of all tests and procedures as well as past contagious and atopic diseases (figures 1 and 2).

The Dick test was performed in 4,640 nurses. Three thousand one hundred and four were found to be negative, and the remainder, 1,536, were positive reactors.

Some of our susceptible affiliate nurses (207) did not take contagious disease training, so that immunization was not compulsory.

* Read before the Twenty-fifth Annual Session of the American College of Physicians, April 25, 1941, Boston, Mass.

From the Division of Contagious Diseases, City Hospital, and the Department of Pediatrics, Western Reserve University, Cleveland, Ohio.

Entrance date (C.C.H.)_____ IMMUNITY RECORD

Date left_____ Date finished_____

Name (Last Name First) | Nursing School | City | State

Small Pox Vaccination						Typhoid-Paratyphoid					
1st Take		Reaction of Immunity				1st Injection		2nd Injection		3rd Injection	
Date	Initials	Date	Initials	Date	Initials	Date	Doctor	Date	Doctor	Date	Doctor

Schick Test-Before Immunization was on Checked by Doctor

Toxin Antitoxin (Toxoid) (Alum. Ppt. Toxoid), Cross out types not used.

1st dose, Date 2nd dose, Date 3rd dose, Date

4th dose, Date 5th dose, Date Reactions:

Shick Test-After Immunization was on Checked by Doctor

Dick Test-Before Immunization was on Checked by Doctor

1st dose Toxin, Date 2nd dose, Date 3rd dose, Date

4th dose, Date 5th dose, Date 6th dose, Date

Reactions (After which dose and type of reaction):

Dick Test-After Immunization was on Checked by Doctor

form 148 (over)

FIG. 1.

Please have physician fill in following blanks. Write "yes" or "no" and give year.

Asthma Hay Fever Type

Hives Strawberry Rash Tomato Rash

Other Food Sensitivities Previous Injections of Serums Antitoxins

Vaccines Disease not mentioned below

Diseases	Year
Measles	
Mumps	
Varicella	
German Measles	
Variola	
Scarlet Fever	
Pertussis	
Diphtheria	
Erysipelas	
Meningitis	
Poliomyelitis	
Encephalitis	
Frequent Colds	
" Sore throats	
Tonsillitis	

Further Record at City Hospital:

FIG. 2.

One thousand three hundred and twenty-nine susceptible nurses were actively immunized; 1,273 by injecting toxins in the old standard doses of 500, 2,000, 8,000, 25,000 and 80,000 units as recommended by the Scarlet Fever Commission; 41 received Larson's vaccine; 15 received toxin made from stock streptococci.

According to the Dicks,[6] 95 per cent of the nurses susceptible to scarlet fever can be immunized. Rappaport[7] reports that 99.5 per cent of 222 nurses became completely immunized after the injection of toxin. He states that since March, 1926 (report made in 1936), no student nurse has developed scarlet fever.

No cases developed among 298 susceptible nurses immunized by Anderson,[8] whereas 15 of 449 nurses who received no immunizing doses contracted scarlet fever during the same period. He and Reinhardt[5] reported 7 failures out of 1,038 nurses immunized. They analyzed the records of over 6,000 individuals and found that the attack rates for the Dick negative group and for the Dick positive group, which was later immunized, were but 0.7 per cent. For the nine years included in their study, the affiliating hospitals that did not provide for immunization had a scarlet fever incidence among their nursing staffs four times as great as that found in the immunized hospitals. Toyoda et al.[9] report that among the non-immunized, 43.3 out of 1,000 persons were infected, whereas among those completely immunized, the rate was only one per 1,000. Henry[10] recalls that in 1926 and for seven years thereafter there were no cases of scarlet fever that developed in physicians or nurses fully immunized. The subsequent Director of Public Health of his city was persuaded to abandon the compulsory immunization program, and the disease again reappeared in the physicians and nurses. Twelve cases developed among the personnel before reimmunization was started. Knights[11] immunized a small number of nurses and decided that the results were encouraging enough to warrant continuing the immunization of nurses who gave no history of having had scarlet fever. In 1934, Benson and Rankin[4] of Edinburg detailed nine years' experience with active immunization. Seven of their nurses contracted the disease, but only one of these had been immunized.

Place[3] reported that the majority of their nurses had been immunized since 1925. The attack rate among susceptible nurses was 8.6 per cent; between 1925 and 1936, the rate among 1,446 nurses serving in the ward was 1.3 per cent or 20 nurses. Only three failures of immunization were described, one of which never became negative even after two series of injections. Two of the three had positive Dick tests, one before and one at the onset of the scarlet fever; one was not tested. It is significant that the drop from 8.6 per cent to 1.3 per cent in this series was not associated with a corresponding decrease of scarlet fever among nurses in general of this region. One hundred and twenty-seven nurses became ill with scarlet fever and were admitted to the hospital between 1913 and 1924; during the next

12 years, there were 100. This decrease in the number of scarlet fever cases among the nurses was not due to the fact that there was a decrease in the incidence of scarlet fever; in fact, the morbidity had increased.

Not one of Platou's [12] 164 immunized susceptible nurses had scarlet fever during a period of four years, whereas the disease developed in eight out of 150 non-affiliated students.

Hektoen and Johnson [2] state that not one of 200 immunized susceptibles developed scarlet fever and that of 614 nurses taken into the Service since the Dick test came into use, three or 0.5 per cent had scarlet fever. Only one of their nurses developed scarlet fever since December 1, 1927 (report 1934).

Results of Active Immunization at City Hospital, Cleveland

Not all of the 1,273 individuals immunized received the full five doses as recommended by the Scarlet Fever Commission (table 1); 155 had from one to four doses; 1,118, five or more. Immunization was discontinued and the nurse received less than five doses if the reactions became too severe, if she returned to her own school or for many other reasons.

Active immunization against diphtheria as well as scarlet fever is sometimes condemned because individuals previously injected with vaccine antigens have contracted the disease. Such condemnation is never merited if no effort has been made to find out whether the susceptibles have been immunized. The only way one can be sure that a patient has been immunized is by doing a Dick test after the immunization procedure has been completed.

The results of immunization are contained in table 1.

Table I

Immunization

Total Number Nurses to Be Immunized	1273	Total Number of Negative Reactions After Immunization	1181
Only 1 dose given	6	Negative after 1 dose	1
Two doses given	46	Negative after 2 doses	34
Three doses given	49	Negative after 3 doses	31
Four doses given	54	Negative after 4 doses	33
Five doses given	1118	Negative after 5 or more doses	1082
(29 given 2 series of injections)		Still positive	92

Eleven hundred and eighty-one or 92.7 per cent of the 1,273 susceptibles became negative reactors. Ninety-two or a little over 7 per cent were still positive.

Frequently, when the Dick test is repeated in immunized individuals, it may be found supposedly positive and about it will be an area of redness and induration. Sometimes, a second immunizing series may be given and still the reactions are positive, often with marked local reactions. Many of these results are spurious. When such people are tested with control as well as Dick toxin, it may be found that the marked local reactions are due to the control rather than to the toxin itself and that the individuals actually are

negative even though they do have a marked local reaction around the injection.

When, for some reason it became necessary to stop immunization short of five doses, a skin test was done at the same time it would have been performed had the nurses continued with the group in which they had started. One of the six receiving one immunizing dose had a negative reaction. Of the 155 receiving only from one to four doses, 99 seemed to have had some benefit since they became negative reactors. This does not mean that they were completely immunized; they may have been merely immunized against at least one skin test dose.

Sixty-five of the susceptible nurses contracted scarlet fever, 49 of them becoming ill during the course of immunization. Actually, only 16 given the full dose of antigen recommended developed the disease (table 2).

TABLE II

Number Developing Scarlet Fever

During interval between positive test and planned first immunizing dose	41
After one dose	2
" two doses	4
" three "	2
" five " or more	16

Ignoring the 49 who developed scarlet fever during or before immunization was started, there were 16 cases, or a little over 1 per cent of the total 1,273 individuals immunized, who developed the disease.

On admission to the hospital, eight of these nurses had acquired some immunity and were negative reactors to the Dick test; eight were still positive.

The case histories of these 16 cases bear analyses (table 3). In seven, the attacks were mild; in three, moderate; in five, severe; in one, the diagnosis was questionable. The reactions to the test bear no relation to the severity of the subsequent attacks of scarlet fever. Actually, eight had not been immunized; thus, there remained eight failures.

REACTIONS

Reactions occur with any kind of an immunizing procedure. Sometimes these may be as severe as the disease itself. It might be considered axiomatic that the more closely the symptoms produced by the antigen products resemble those of the disease, the better is the chance of immunizing the susceptible.

The reactions to scarlet fever immunization are either local or general, or both. In the local category are redness, induration and sometimes an erysipeloid inflammatory reaction around the point of injection, lymphangitis, local adenitis, pain on activating the arm, fever, etc. The Dicks [6] believe that the more highly susceptible an individual is, the more apt is he to have a

TABLE III

Nurses Who Developed Scarlet Fever and Who Had Five or More Doses of Scarlet Fever Toxin

Name	First Test	Other Tests	Immunized	Date of Scarlet Fever	Type of Disease
D. R.	pos. 12/28/33	neg. 4/12/34	5 injections	4/11/34	severe
M. H.	pos. 1931	neg. 1/11/32; pos. 2/9/34; neg. on discharge	5 "	2/8/34	mild
M. S.	pos. 11/12/30	neg. 1/28/31; pos. 12/6/32; pos. 12/27/32	5 "	12/5/32	mild
H. H.	pos. 11/12/30	pos. after last injection; neg. 11/28/32	7 " (stopped because of reactions)	11/27/32	mild
W. C.	pos. 1930	neg. 10/28/30; pos. 12/4/31	5 injections (severe reaction, 1930)	12/3/31	severe
I. M.	pos. May '31	neg. 10/25/32; neg. 4/1/33	5 injections	3/31/33	mild
L. A.	pos. 1936 pos. 1937	pos. 10/14/38	10 injections (2 series)	10/13/38	severe
S. M.	pos. Sept. '32	neg. 12/19/32; neg. 2/28/33	5 injections	2/27/33	moderate
R. R.	pos. 1934	pos. 1/22/35	5 "	1/21/35	severe
E. S.	pos. 1/19/38	pos. 1/4/39; pos. 7/14/39; pos. 10/3/39; pos. 10/28/39; pos. 2/12/40	10 "	10/27/39	mild
L. H.	pos. 5/5/38	neg. 8/8/39; neg. 11/15/39	6 "	11/11/39	mild
E. L.	pos. 10/1/36	neg. 5/20/37; neg. 4/28/38; neg. 1/3/39	8 "	1/6/38	severe with complications
C. S.	pos. 7/30/32	neg. 9/28/32, 1/1/33 and discharge	5 "	12/31/32	moderate
M. W.	pos. 2/2/32	pos. after 5 doses	5 "	4/11/32	moderate
H. T.	pos. Oct. '34	pos. after inj.; pos. 11/26/31	5 "	11/25/32	mild
R. S.	pos. Feb. '29	pos. 2/22/32; pos. on discharge; pos. 8/5/39	5 "	2/21/32	possible S.F.

reaction after the first dose. It has been difficult for me to tell which of the five doses would cause a reaction; nor have I been able to foretell what kind of a reaction to expect. Sometimes reactions will occur about superficially injected toxin.

General reactions include malaise, nausea, headache, high fever, a scarlatiniform rash, vomiting, diarrhea, adenitis, arthritis, etc. An arthritic, in my experience, is never desensitized by repeated injections of scarlet fever toxin to the point where he may not have reactions following subsequent increased injections of the toxin. Arthritis, occurring during active immunization is due to the toxin (Healey [13]). Sometimes, when it is injected deeply, absorption will take place too quickly and cause general symptoms. Benson and Rankin [4] reported that 14 per cent of 143 nurses immunized had constitutional symptoms.

The total number of reactions in the group from City Hospital, Cleveland is noted in table 4.

TABLE IV
Reactions

	Doses					Total No.
	1	2	3	4	5 or more	
Reactions	58	77	84	77	68	364
Local	11	7	6	11	3	38
General	47	70	78	66	65	326

Number of nurses having reactions 131 (10.2%).

One hundred and thirty-one or 10.2 per cent of the nurses injected had reactions at some time or other. Rappaport [7] reported that 80 per cent or 31 of the nurses in the class of 1931 and 100 per cent or 35 in that of 1932 had reactions after the five doses of toxin. Between 1924 and 1935, he tested 439 nurses, of whom 249 or 56.7 per cent were found susceptible and immunized. He then started to inject smaller amounts more frequently. He began with 150 skin test units; the subsequent doses were 300, 600, 1,200, 2,500, 5,000, 10,000, 20,000, 40,000 and 80,000 skin test units for each dose, respectively—a total of 159,750 skin test doses or 38.3 per cent more toxin than when the usual five doses (standard doses prior to 1940) were given.

The amount of skin test doses of toxin now recommended by the Scarlet Fever Commission and injected subcutaneously is as follows: 650, 2,500, 10,000, 30,000 and 100,000 skin test doses. If the patient has a severe reaction to the initial dose or to the skin test, the subsequent injections should be decreased in amount and the number of injections increased. Adrenalin is sometimes given with the toxin in doses of about 0.2 c.c. to 0.3 c.c. of a 1:1000 solution. In a highly sensitive individual, one may start with one-fourth and increase to one-half of the original recommended dose, the next

time going back to the initial dose. If at any time there is a marked reaction, it might be advisable to revert to the last standard dose and then to start again with a quarter of that recommended. Each such susceptible is an individual problem.

Negative Dick Tests and Development of Scarlet Fever

Seventy-six nurses were admitted with scarlet fever who had had negative Dick tests from one day to five years prior to contracting the disease (table 5). This was 2 per cent of the negative reactors.

Table V

Interval after Test Disease Contracted	No.	Interval after Test Disease Contracted	No.	Interval after Test Disease Contracted	No.
1 day	2	1 month	9	1 yr.	6
2 days	4	2 months	12	1 yr., 1 mo.	1
3 "	1	3 "	11	1 " , 2 "	1
4 "	2	4 "	2	1 " , 6 "	2
5 "	1	5 "	4	1 " , 8 "	2
7 "	1	7 "	7	2 "	3
14 "	1	8 "	2	2 " , 5 "	1
				5 "	1

Despite their previous reports, the 76 individuals previously found negative were again Dick tested on admission to the hospital. Eight reactions could not be read accurately because of the rash; 25 had lost their immunity and were definitely positive reactors on admission, while 43 were still negative. This would give a corrected morbidity of 1 per cent in the exposed negative reactors. There may be some question about the results with one test dose, so that for the sake of accuracy, they were also tested to one, two, three and five skin test doses and found to be negative.

There are many reasons why a Dick test may be negative and erroneously so. This could explain some, but certainly not the majority of aberrant results. A negative reaction may occur if the Dick test material is not up to standard because it has not been kept properly and in accordance with the specifications.

There is only a minute amount of toxin in the skin test dose. This small amount may be easily neutralized or destroyed by some factor—soap, alcohol, iodine and the like. The skin test is a quantitative one, indicating the presence of a certain amount of antitoxin in the blood stream; thus, quantitative exposure greater than the usual may initiate scarlet fever in an individual who has protection against the ordinary doses of antigen to which he would customarily be exposed.

In doing a Dick test the skin must be dry and cleansed of alcohol and other disinfecting agents. Needles and syringes must be absolutely dry; the water in the barrel and needle should be blown out. Needles and

syringes should not be boiled in tap water. The dose of toxin must be accurately measured. The injection should be into the skin, and it should be read at the proper time. All the factors compared should be the same under all given circumstances.

The Dicks [6] reported 20,956 persons with negative Dick tests, who, with but one exception had gone through at least one epidemic without contracting scarlet fever. Platou [12] collected reports on 20,000 immunized individuals and found that only one had developed the disease.

Speaking of failures to immunize, Anderson and Reinhardt [5] stated that no biological phenomenon is mathematically exact, and that similar figures are encountered in dealing with other immune reactions.

Does the Toxic Antigen Protect Only Against the Rash?

Some individuals feel that all that is accomplished by giving scarlet fever toxin is to immunize against the toxin that produces the rash. They feel that immunized persons may still become ill with streptococci which cause scarlet fever. In fact, some believe that the number of colds, sore throats, etc. in this group is increased. As Place [3] states, "whether the standard toxin will protect immunized persons against most clinical effects of scarlet fever and especially whether such immunized persons are protected against infection or only against the toxin" can be determined only by collective experiences under actual conditions of exposure. My own experience, however, has been quite fortunate. There is a rule at the City Hospital, Cleveland to the effect that nurses and all other personnel on any service contracting a sore throat or any upper respiratory infection are immediately isolated in the Contagious Disease Hospital. This has given me an opportunity to evaluate the results, and I can definitely conclude that there has been no increase in the number of nurses who have contracted scarlet fever or who have contracted streptococcic sore throat; in fact, I think there has been a very definite decrease. Only during epidemics, has there been a marked increase in the number of such patients admitted, and then we have those irrespective of whether they have been immunized or not. It is my impression that there has been a decrease in the number of nurses who have developed these types of acute upper respiratory infections.

Benson and Rankin [4] gave definite figures on this point and concluded that there was no increase in the incidence of tonsillitis during an observation period from 1919–1933. In the 12 years before immunization, Place [3] had 65 nurses, or 6.4 per cent, admitted with streptococcus infections other than scarlet fever; since immunization, there were 67 or 4.6 per cent.

How Long Does Immunity Last?

Anderson and Reinhardt [5] state that immunity lasts at least three years. Our experiences do not extend beyond three years, after which nurses leave the hospital, and we lose control of the individual. In a small series (100)

we have been able to do Dick tests five years after a negative Dick test had been produced and have found that approximately 72 per cent were still negative. We have personal knowledge of an orphanage where the children have been immunized and where they have gone through several epidemics. The time interval has been at least 9 or 10 years, and the resident population still seems to be immunized and protected. If it is realized that there is a process of natural immunization constantly going on in children and that at least 65 per cent of adults may be immunized by the time they are between 20 and 30 years, it will be seen that an immunization procedure which protects children in the younger age group (from 5 to 6 years) may be sufficient to give them enough immunity so that with the additional stimulus obtained from frequent exposure, they may become permanently immunized against this disease. The Dicks [6] state that the duration of immunity lasts approximately 12 years (90 per cent).

Do Immunized Individuals Become Carriers?

This question is easily answered. The best place in the world to ascertain the presence of a carrier state is in a contagious disease hospital where there is a constant chance for the exposor to contact exposees, a most severe experimental test. If nurses were made carriers then we should have an increase in the number of scarlet fever cross infections in the contagious disease hospital. No other hospital has reported an increase, and we actually have had a decrease in hospital cross infections.[14]

Larson's Scarlet Fever Toxoid

Another type of antigen used to immunize against scarlet fever is ricinoleated toxoid introduced by Larson and his associates in 1926.[15] They reported 77.3 per cent of positive skin tests becoming negative in eight days and 97 per cent in three weeks after the use of this antigen. Some of this vaccine material was obtained from Dr. Larson in 1926 and tried in a group of 41 nurses. The results are contained in table 6.

Table VI

Larson's Antigen (first dose 0.5 c.c.; all others 1 c.c.) 41 susceptibles

	Reaction to Dick Toxin
41 received 1st and 2nd doses	15 neg. 3 weeks later
26 remaining received 3rd and 4th doses	10 " 8–9 " "
16 remaining received 5th and 6th doses	5 " 3 " "
11 remaining received 7 to 17 doses	3 "
	6 persistently positive

Two nurses who were negative reactors to the Dick test and had been immunized with Larson's toxin contracted scarlet fever; one had a mild attack; the other died. The histories of the two who contracted scarlet fever are outlined in table 7.

Protection was established in some of the susceptibles injected. The experiment was discontinued, however, because the reactions seemed nearly as severe as those following the Dick toxin, and the immunizing results were no better.

TABLE VII
Larson's Vaccine

Name	First Test	Other Tests	Immunized	Date of Scarlet Fever	Type of Disease
I. M.	pos. 8/5/26	neg. 11/8/26	13 injections	1/9/27	Mild
E. K.	pos. 10/4/26		5 "	1/25/27	Died; hemorrhagic

GABRITCHEWSKY'S VACCINE

This is a mixture of killed streptococci and streptococci toxin. Benson and Rankin [4] refer to several workers who used this material (Mstibowsky, Korschun and Spirina, Hoffmann, Sparrow, Zlatogoroff). The impression gained is that the morbidity and mortality rates of scarlet fever were lessened after its use. Zlatogoroff concluded that the vaccination had a favorable effect on both morbidity and mortality, but that this was short lived.

VELDEE'S FORMALINIZED TOXIN

Veldee [16] has reported favorably on formalinized toxin. Futagi,[17] using a toxoid, reported that over 84 per cent of a group of susceptibles given four injections of the solution were rendered Dick negative. Formalinized toxin was used by Anderson,[8] who found that it caused so few reactions that it has been accorded a ready and popular acceptance in all groups to which it has been offered. He concluded that it had an appreciable immunizing value as measured both by Dick tests and by protection against clinically recognized scarlet fever. He felt, however, that this immunizing effect was not as great as that which followed the use of the standard five injections of Dick toxin. He concluded that as administered it is a less potent immunizing agent than Dick toxin, for only about 50 per cent of those susceptibles treated with formalinized toxin are rendered Dick negative in contrast to 90 to 95 per cent after the Dick toxin. Benson and Rankin [4] believe that toxins tend to lose their antigenicity when formalinized.

STREPTOCOCCUS TOXINS

Park and Spiegel [18] stated that it was quite possible that there were strains of streptococci which had the power to produce scarlet rash-producing toxins different from the standard Dick strains. Kirkbride and Wheeler [19] reported on a person found susceptible to the Dochez toxin and not to the Dick or Williams toxin.

When the Dick test was first used by us in the Division of Contagious Diseases, City Hospital, Cleveland, a test was done in each scarlet fever patient on admission to the hospital. A positive test would invariably become negative within a month. In 1929, the results of the skin tests done on scarlet fever patients on admission were erratic. In 1933, the number of positive reactors became higher, but still there were many exceptions. Perhaps we dealt with epidemics caused by different strains of streptococci.[20] This would explain why nurses with negative Dick tests, nevertheless, develop scarlet fever.

It has been stated that the streptococci causing scarlet fever and erysipelas must be different, because clinically, erysipelas is a different disease from scarlet fever, although both are caused by streptococci. This conclusion does not follow. Erysipelas frequently follows, but rarely precedes

TABLE VIII

Nurses Who Had Streptococcus Toxins and Who Developed Scarlet Fever

Name	First Test	Other Tests	Immunized	Date of Scarlet Fever	Type of Disease
H. H.	pos. 2/2/32	pos. Dec. '31; pos. 4/4/32; pos. 5/12/32; neg. on discharge	5 injections	5/11/32	severely ill
V. B.	pos. 10/13/31	neg. 1, 2 and 5 skin test doses after injection; neg. 12/31/31	6 "	12/30/31	mod. severe
R. G.	pos. 1/19/32; pos. 2/2/32	pos. after 1932; pos. Feb. '32; pos. 3/23/32	5 "	3/22/32	severe
E. H.	pos. 10/5/31	neg. 1/11/32; pos. 2/2/33; neg. on discharge	6 "	2/1/33	mod. severe
A. N.	pos. 2/2/32	pos. after injection; pos. 3/31/32	5 "	3/30/32	moderate
D. R.	pos. 2/2/32	neg. 4/4/32; neg. 6/14/32	5 "	6/13/32	mod. severe
V. C.	pos. 10/13/31	neg. 1/8/32; neg. 1/23/32	6 "	1/22/32	severe

scarlet fever. There is antitoxin in the blood serum of erysipelas patients at the very time they get erysipelas. The clinical entity called erysipelas can best be explained by stating that it is really nothing more than a local, massive, allergic type of reaction occurring in an individual who has plenty of immunity against the streptococci, but who is sensitive to the protein products of the streptococcus organism.

It was decided to manufacture toxin from other strains and to determine if they could be used in immunization. Ten strains were used, including two Dick and one Dochez. Each strain was planted in 14 flasks of 0.5 per cent glucose broth. This was repeated daily for 14 days. Twenty-four hours after the first inoculation and daily thereafter, the toxin contained in one flask from each culture growth was harvested. There was great difficulty in standardization, but the conclusions were obvious. The Dick and Dochez strains produced a highly potent toxin in a very short time (24 to 48 hours).

Other strains, like those of Birkhaug (erysipelas) (three of four strains), also produced a toxic factor, but in no appreciable quantities until six or seven days had elapsed. All of the organisms produced toxin, some earlier than the others.

Two toxins were made up in large batches—No. 420 (Crook's strain from puerperal infection) and No. 624 (Frost's strain from septic sore throat). We attempted to standardize the toxin by skin test dosage in the same fashion as the Dicks standardized their material. The technical accuracy of our standardization procedure was not completely satisfactory in that our standard solutions were probably understandardized as compared with the Dick material. However, the results were suggestive and in the right direction.

Fifteen volunteer susceptibles were injected with five doses of the combined material; seven were still positive to the Dick test and eight had become negative within one month after the last injection. Seven of these individuals contracted scarlet fever; one of the seven might have had a rash due to the toxin injection, since it occurred 24 hours after the fifth injection (table 8).

That we had immunized some positive susceptibles to a degree, at least, is seen from the fact that on admission to the hospital four of the seven patients who contracted scarlet fever were negative not only to one, but to two and three skin test doses of Dick toxin; three were still positive on admission. No definite conclusions can be drawn from this work. It only suggests the fact that probably all streptococci produce toxins.

Oral Vaccination

Because of the reactions following the use of naked scarlet fever toxin, some experimentation has been done by the Dicks [21, 22] on oral vaccination. An average of 75 million skin test doses of toxin was recommended as the immunizing dose, starting with 100,000 and increasing to 6 to 10 million skin test doses a day for the last three to six days. Of 17 individuals in one group, 11 were immunized. In another group of 102 persons, 98, or 94.7 per cent, were immunized.

This method of vaccination is in the experimental stage. If it proves satisfactory, the objection to scarlet fever immunization on a wholesale measure will be materially lessened.

Comment

The recent Army Bulletin No. 81 [23] recommends that active immunization should be given to nurses with positive reactions to Dick tests and for orderlies assigned to care for patients with scarlet fever. It was not recommended for general use to the Surgeon General because there is a "high percentage of immune subjects among adults, and because at least 5 or more injections are usually required to produce immunity."

Susceptible young adults in contagious disease hospitals contract the disease because of massive exposure, etc., and it has been proved repeatedly that these individuals can be protected. It is equally obvious that where there is crowding and disease occurs, as in the army, cross infections will follow. It is not clear why susceptible exposees in the army should not be immunized.

In pediatric practice, the only reason the vaccine may not be used is because of the reactions; but physicians, especially pediatricians, can easily immunize their patients, especially if they appreciate the reactions and avoid them by injecting a greater number of smaller doses.

Conclusions

1. Susceptible adults are easily immunized with scarlet fever toxin to the point where they will have a negative Dick reaction.
2. Eight nurses successfully immunized to a negative Dick test developed scarlet fever, an attack rate of 0.6 per cent.
3. Active immunization against scarlet fever has become a standard procedure in most hospitals for contagious diseases.
4. Active immunization, though not a public health measure as yet, can be used by private physicians in their practice, provided they take precautions to avoid complications.

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THE TREATMENT OF ACUTE EMPYEMA; TREATMENT BY CONTINUOUS TIDAL IRRIGATION AND SUCTION (HART) *

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The method of treating acute empyema by tidal irrigation and suction, described by Hart,[1, 2, 3, 4, 5, 6] was introduced in 1929 on the medical and surgical services of the Sinai Hospital, and since that time 33 cases have been treated by this procedure. In four of these, tidal drainage was insufficient and was followed later by rib resection and thoracotomy; they will be discussed separately later in this report. In 30 of the 33 cases, the operative procedure was performed and the subsequent course was followed personally by the senior author.

Technic. The details of the method, operative and postoperative, have been clearly given by Hart,[6] and we followed them closely. In all our cases (including those with a broncho-pleural fistula) we used the apparatus as described and illustrated in his paper in 1935.[6] We did not follow closely enough his directions for the case of the bronchofistula in our series. As a result of our own experience we wish to make the following suggestions about the care of the apparatus which we think may be helpful.

To prevent leakage, especially in children, it proved advisable to secure the tube in the chest snugly. This was accomplished by tightening the adhesive on the front of the chest after the patient was turned on his back (the adhesive having been first applied with the patient on the sound side). Also, to prevent excess pulling on the tube by the nurse when she changed the bed linen, we allowed an increase in the length of the tubing leading to the irrigating bottle. Apparently this did not interfere with the force of the irrigation.

To prevent air from entering through the flask containing the fresh fluid, we marked the flask to indicate a point beyond which the fluid level was never allowed to fall.

Thick pus and fibrin did not give us much concern, especially if we aspirated most of the thick pus and irrigated the cavity at the time of the thoracotomy and before we attached the bottles. If plugging did occur, it was only temporary and the plug could always be dislodged without disconnecting the apparatus.

Some cases demand more attention than others. It is an advantage to have personnel familiar with the operation and care of the apparatus. We found nurses more suitable than house-officers because the former are more permanent in their positions.

The tube in the chest can be withdrawn at one time if complete suction has been maintained for about five days. The shortest length of the tube in the chest to give proper irrigation measured between 4½ and 5½ inches.

The chief chance of complication developed at the time of the insertion of the trocar. Preoperative roentgen-rays should always be taken in order to locate if possible the height of the diaphragm. Great care should be exercised in locating

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the proper interspace and it is probably safer to go a space higher than in the reverse direction.

Of the 33 patients treated, six died, i.e., a mortality of 18 per cent. The mortality in the 29 patients treated by closed drainage alone was 20.7 per cent (table 1).

TABLE I

Mortality

	No. Cases	Deaths	Per cent Mortality
Tidal irrigation only	29	6	20.7
Tidal irrigation plus rib resection	4	0	0.0
Total	33	6	18.2

There were six deaths in the group of patients treated with continuous tidal irrigation and suction. In three cases, death was directly attributable to acute purulent pericarditis, associated, in one patient, with acute peritonitis. At necropsy, the empyema cavities were almost entirely clear. Two infants, aged 21 and 12 months respectively, were critically ill and almost moribund when they were admitted to the hospital. In both, tidal drainage worked well, but their toxic state could not be relieved. The sixth fatality occurred in an eight year old girl who had unilateral empyema during a fulminating pneumonia which involved all five lobes and which was complicated by acute encephalitis and hemiplegia (table 2).

TABLE II

Fatalities

Age	Organism	Patient's Condition at Operation	Time of Death—Days Postop.	Cause of Death
11 yrs.	Pneumococcus Type IV	Fair	36	Suppurative pericarditis
5 mos.	Pneumococcus Not typed	Poor	2	Suppurative pericarditis
10 mos.	Pneumococcus Not typed	Poor	3	Suppurative pericarditis peritonitis
21 mos.	Pneumococcus Not typed	Moribund	1	Systemic infection
12 mos.	Pneumococcus Not typed	Moribund	4	Systemic infection
8 yrs.	Pneumococcus Type I	Very toxic	7	Encephalitis; hemiplegia; 5-lobed pneumonia

All the patients who died were under the age of 12; four were less than two years old (table 2). In the group under two years of age, the mortality rate was 57 per cent which is high, but it must be recalled that two of these patients died of purulent pericarditis and the other two because of an overwhelming systemic infection; furthermore, the number of patients in this

age group is very small. In all cases, the irrigation apparatus functioned satisfactorily.

The age incidence in the group (29) treated by tidal irrigation alone ranged from five months to 46 years; 22 were under the age of 16 (table 3).

TABLE III

Age Groups

Age	No. Cases	No. Deaths	Days Treatment (Average)
Birth to 6 mos.	1	1	
7 mos. to 12 mos.	1	1	
13 mos. to 24 mos.	5	2	27
2 yrs. to 5 yrs.	6	0	39
6 yrs. to 10 yrs.	5	1	35
11 yrs. to 15 yrs.	4	1	43
16 yrs. to 20 yrs.	1	0	48
21 yrs. to 30 yrs.	3	0	46
31 yrs. to 50 yrs.	3	0	23
	29	6	37

The "average duration" of treatment (37 days) comprises the time interval between the institution of drainage and the final withdrawal of the tube.

Bacteriological studies show that no patient with streptococcal or staphylococcal empyema died, which is in agreement with Hart's observations.[4] All six of the deaths occurred in patients who had pneumococcal empyema: one type I, one group IV, and four in whom the pneumococci were not typed (table 4).

TABLE IV

Organisms

Organism	Number of Cases	Number of Deaths
Pneumococcus		
Type I	8	1
Type II	0	0
Type III	2	0
Group IV	5	1
Not typed	10	4
Staphylococcus		
albus	1	0
aureus	1	0
Streptococcus		
hemolyticus	2	0

Almost all of our patients had extensive, free empyema which was drained easily. In two patients with bilateral empyema, the fluid was pocketed on one side, but there was no interference with irrigation. In two infants who died of acute suppurative pericarditis the empyema drained was encapsulated in a single large pocket, and in both necropsy demonstrated that the pleura elsewhere was clear. One 39-year-old patient, with right-sided interlobar empyema, had complete closure of the cavity in 12 days.

Twenty-three of the patients had pneumonia affecting more than one lobe. Fourteen had consolidation of two lobes, and seven had lesions involving three lobes (table 5).

TABLE V

Lobes Involved

Number of Lobes Involved	Patients	Recovered	Died
1	6	5	1
2	14	12	2
3	7	5	2
4	1	1	0
5	1	0	1

During the period that this method of treatment of acute empyema has been employed at this hospital, open drainage has also been used. The medical service has endeavored to select those cases for tidal drainage that would profit best by this procedure, and has, at the same time, advised open thoracotomy for many patients who appeared to require that operation.

In reviewing these cases, several major indications for tidal drainage become apparent and these may be summarized as follows:

	Number of Patients
Condition too poor for rib resection	4
Streptococcal empyema	2
Synpneumonic empyema	12
Bilateral empyema	3
Broncho-pleural fistula	4
Septicemia with synpneumonic empyema	4

Under tidal drainage the temperature ordinarily returned to normal within three or four days after the irrigation was begun. However, in the four cases with broncho-pleural fistula complicating pneumonia, elevations of temperature persisted from two to three weeks after drainage was instituted. In some instances slow resolution of the pneumonic process resulted in pyrexia beyond four days; in one case there was a recrudescence of the pneumonia, and in another, a dissemination of the pneumonia to the contralateral side. "Catheter fever," so-called because it is caused by a plugging of the tube by clumps of fibrin, occurred occasionally, but was readily corrected by mechanical flushing or irrigation with Dakin's solution.

Broncho-Pleural Fistula. In the treatment of broncho-pleural fistula, tidal drainage was very effective, although the results obtained in this series were not as spectacular as those reported by Hart.[2, 3] In almost all of the latter's cases, the fistula closed within 48 hours. In our series (table 5) closure was not effected until a much longer period had elapsed, probably for the reason already mentioned; when closure did take place, however, the healing was permanent. The series included four cases, without a single mortality.

Bilateral Empyema. Recovery followed tidal irrigation in three cases of bilateral empyema. In this group the results were more satisfactory than

those noted by Hart,[2, 3, 4] and are reported in detail below. All three patients had bilateral pneumococcal empyema, one due to Type I pneumococcus and two due to infection with group IV pneumococci.

TABLE VI
Broncho-Pleural Fistulae

Patient	Age	Duration of Empyema—Days	Duration of Fistula—Days Before Irrigation	Closure Days—Postop.	Irrigation Total Days
R. E.	18 mos.	3	2	20	32
N. J.	2 yrs.	5	5	62	71
D. S.	3 yrs.	8	7	11	32
C. K.	21 yrs.	8	4	12	47

In one case, N. J., the pneumothorax was present before any diagnostic needling was done; in the others it was detected only after diagnostic thoracenteses.

R. R., two years old, was admitted February 24, 1936, with acute otitis media. Three days later signs of pneumonia of the left lower lobe developed, followed in 11 days by signs of empyema (March 9). Four days after the left-sided pneumonia became manifest, signs of consolidation of the right lower lobe were detected, and signs of empyema appeared seven days later (also March 9). Tidal drainage was instituted on the right side two days after the discovery of the effusion there, and the fluid was found to be pocketed. The temperature fell to normal within 48 hours, but rose again within a few days, and on March 20 tidal drainage was begun on the left side, where the fluid was free. Both irrigation apparatuses worked satisfactorily and were run simultaneously throughout the course of the illness. Drainage and irrigation were maintained for 52 days on the right side; for 30 days on the left side.

G. P., six years old, was admitted November 23, 1929, with pneumonia of two days' duration, involving the right middle and lower, and the left lower lobes. Fourteen days after the onset of the illness signs of bilateral empyema became evident. Tidal drainage was begun on the left side four days later; on the right side after an interval of seven days. The course was complicated by an acute pyelonephritis and by a recrudescence of the left lower lobe pneumonia, but continuous irrigation was uninterrupted. Total days of irrigation: right side—31, left side—37.

G. H., seven years old, was admitted on October 30, 1933, with pneumonia involving the right upper, middle, and lower lobes, of five days' duration. Three days later, signs of empyema appeared. After three aspirations, tidal drainage was begun, eight days after discovery of the empyema. Two days after the institution of continuous drainage, pneumonia of the left lower lobe developed, followed in 14 days by empyema on that side. Tidal drainage was started within 24 hours, both apparatuses functioning concurrently. The subsequent course was satisfactory. Total days of irrigation: right side—51, left side—32.

As can be seen from table 7, many of the patients included in this series developed serious complications, frequently rendering treatment of any kind difficult and prolonging the period of hospitalization. Most of the complications could not be attributed to the method of therapy; but it was evident, as noted by Hart,[2] that precautionary measures can minimize the occurrence of at least three untoward events. These are: (1) Reformation of the cavity, because suction is removed too early; (2) pocket formation, because suction is applied too rapidly; and (3) osteomyelitis of a rib.

There were four patients in whom, for various reasons, rib resection and thoracotomy were performed after preliminary tidal irrigation and suction.

One patient, an acutely ill 61 year old man with severe diabetes, was carried safely over an old interlobar empyema by tidal irrigation for two months. Because of the rigid walls, the cavity could not be reduced to less than 15 c.c. capacity. Rib resection and removal of the roof of this cavity were followed by complete recovery within a year.

TABLE VII
Complications

	Total	Recovery	Deaths (6)
Not referable to treatment:			
Bilateral empyema	3	3	0
Bilateral pneumonia	11	8	3
Pericarditis	3	0	3
Peritonitis	1	0	1
Septicemia	9	9	0
Encephalitis	1	0	1
Otitis media	7	4	3
Broncho-pleural fistula	4	4	0
Metastatic abscess	1	1	0
Periarthritis	1	1	0
Pyelonephritis	2	2	0
Furunculosis	1	1	0
Myocarditis with cardiac insufficiency	3	2	1
Osteomyelitis of rib (secondary to trauma before admission)	1	1	0
Subcutaneous emphysema, infected (preoperative)	1	1	0
Referable to treatment:			
Reformation of cavity, suction removed too early	1	1	0
Pocket formation, suction applied too rapidly	3	3	0
Osteomyelitis of rib	1	1	0

In a 27 year old woman, from whose pleural fluid pneumococcus Type III and *Hemophilus influenzae* were cultured, the empyema reformed because suction was removed too early. After open thoracotomy was done she convalesced uneventfully and was completely healed six months after rib resection.

There was one patient in whom tidal irrigation was unsatisfactory from the time it was instituted. This was a young man of 23, who was found, after rib resection and wide exposure of the thoracic contents, to have postpneumonic lung abscesses (hemolytic *Staphylococcus aureus*), with multiple empyema pockets. Another patient, a 45 year old woman, developed a complication which might be considered the result of a technical error. Pus had been obtained with the aspirating needle placed supposedly in the right eighth interspace. On insertion of the trocar, however, pus was not obtained. A roentgen-ray film then showed a high diaphragm with the catheter in the ninth interspace. Failure to take a film before thoracentesis certainly contributed to this error. She developed a subphrenic abscess,

presumably as a result of the perforation of the diaphragm, but recovered completely after a rib resection for the drainage of the empyema and after another one subsequently for the drainage of the subphrenic abscess.

Summary and Conclusions

During a period of nine years, 33 patients with acute empyema have been treated by closed drainage, with continuous irrigation and suction (Hart). The mortality rate in the entire series was 18 per cent; in the 29 cases treated by irrigation and suction alone (without subsequent open drainage), 20 per cent. The six deaths that occurred were due to pre- and post-operative complications, and were in no way related to the mode of treatment. No patient with streptococcal or staphylococcal empyema died.

Tidal irrigation functions equally well in the presence of thick or thin pus, provided the person responsible for the management of the apparatus is familiar with the technic of removing clumps of fibrin from the drainage tube which may become plugged in those cases in which thick pus is found.

The indications for closed drainage by the Hart method are reviewed.

Tidal irrigation and suction were found to be effective in four cases of broncho-pleural fistula and in three cases of bilateral empyema, without a death in either group.

Complications due to the method of treatment are noted, particularly in two patients in whom tidal drainage was followed by rib resection and thoracotomy.

None of the patients treated by tidal drainage alone developed chronic empyema or a persistently draining sinus.* Two adult patients developed chronic empyema following tidal irrigation supplemented by rib resection, one healing within six months, the other within one year.

The closed method of treating empyema requires the constant personal attention of the operator. If he is not willing to give this he should not employ the method. The technic and the care are simple and easily learned after several patients have been treated.

Dr. Deryl Hart set up and supervised the treatment in several of the early cases herein reported. We wish to take this opportunity to express our appreciation of his kindness.

Our thanks are gratefully extended to Dr. Charles R. Austrian for his encouragement and advice in the preparation of this report.

* One patient, F. R., was admitted first in 1935, at the age of 18 years, with a massive empyema on the left side; at that time the empyema was apparently successfully treated by tidal irrigation. She ran a smoother course than any other patient (according to notes on her chart) previously so treated. Her temperature never went over 100° F. On that admission she gave a history of rib resection for left sided empyema at three years of age.

Since this report was written she was readmitted July 12, 1938 with a draining chronic left empyema which had been operated upon at another hospital in another city. On July 20, 1938 her left chest was explored after resecting part of the seventh, eighth, and ninth ribs. Recovery was slow and she healed down to another chronic sinus. On January 5, 1939 the chronic pleurocutaneous sinus tract was excised. She was finally discharged on January 26, 1939 with wound healed, having had a normal temperature for 10 days.

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CHEMOTHERAPY OF BACTERIAL ENDOCARDITIS*

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THE treatment of bacterial endocarditis by chemical agents has been under consideration for many years, and the literature before sulfanilamide contains many reports of cures.

The reproduction of the disease in dogs [1, 2, 3] and its cure following the use of merthiolate intravenously [4] and sulfanilamide orally [4] created a hope that such agents could be successful in human cases. With the failure of merthiolate and the extended interest in the use of sulfonamide drugs in other fields of coccal infection, there has been renewed study of the use of these sulfonamide drugs in all forms of bacterial endocarditis.

A glance at the literature of the past few years reveals many reports of cures,[5-17] but curiously, many times as many failures, and of course only a small fraction of the number of failures is reported. This fact leads to a more critical attitude with regard chiefly to the validity of diagnoses in those cases reported as cures. For example, if a patient known to have a valvular heart disease becomes febrile during the puerperium and displays a positive blood culture which is removed following sulfanilamide, the case may still have been not one of endocarditis, but perhaps only of pelvic cellulitis.

If there were a certain cure for bacterial endocarditis now there would be no need for further discussion. But practitioners all over the country have attempted to repeat the allegedly successful methods in their own cases, and having met with failure, approach the discussion with open mind and with some skepticism.

The Diagnosis. Every clinical report should reveal the evidence on which the diagnosis is based. The diagnosis cannot be established by declaration. The evidences of bacterial infection of the heart valve are:

1. *Toxemia.* This point has been well emphasized by Christian [18] in a recent paper. Toxemia is evidenced by fever, weakness, pallor,[19] and deterioration of the blood.

2. *Increasing evidence of valvular defects.* The increase in evidence is very important. Not only must murmurs be detected, but these murmurs must be getting more coarse in quality week by week. The speed of increase is marked in acute endocarditis, slow but definite in subacute endocarditis. Those rare cases of vegetations which form on the wall of the aorta or pulmonic artery can be excluded from this discussion.

3. *Bacteremia.* It is important that the blood culture be constantly positive. In rheumatic cases in which there is a bacteremia the colony count is usually low, but the colonies should be identified as belonging to the

* Read at the Boston meeting of the American College of Physicians, April 22, 1941.

same strain of nonhemolytic streptococcus. Too many reports otherwise convincing, describe only one or two blood cultures.

4. Embolic phenomena are common but not always present at the time of observation. The petechiae of the skin and conjunctiva, and the deeper hemorrhagic lesions about the finger tips are the most common. These are assumed to be embolic. Less frequent are the more definitely embolic occlusions in the spleen, kidney, and brain.

5. Finally, a critical exclusion of other sources of bacteremia must be made.

If the literature is now reviewed with these criteria in mind, the number of apparent cures dwindles.

The discussion of chemotherapy is linked with the discussion of pathogenesis.[20] It is not necessary to be controversial on this point since it is probably true that as the disease is produced, so it is to be cured. In other words, the route used by the bacteria can also be used by the chemical agent. But pathogenesis has a bearing on the relation of fibrin to the bacteria, and so is worth considering in view of the alleged importance of fibrin in defeating the effect of treatment.

The idea has been advanced that fibrin protects the imbedded bacteria from the action of drugs.[3] This was the basis for using heparin in an effort to prevent the formation of this protective fibrin.[21, 22] The subsequent use of heparin met with failure.

There is another idea [23] that the vegetation develops as a result of bacterial plugging of fine capillaries in the previously damaged valve and then builds up from the interior of the valve and breaks through the necrotic material onto the free surface of the valve where some blood-stream fibrin deposits on its surface.

Studies of vegetations both in human and in experimental [4] cases seem to support the idea that the bacteria causing the infection of the blood stream are not those imbedded in the mass of pink-staining material, but rather the bacteria spreading upon the endocardial surface uncovered by fibrin. This would give fibrin a more beneficent rôle as far as the patient is concerned, and would support the theory that the formation of fibrin should be encouraged rather than prevented.

In the medical service at the University Hospital of St. Louis University in the past three years there have been 28 cases of acute and subacute bacterial endocarditis treated with chemical agents. It has frequently happened that blood cultures were sterilized by both merthiolate and the sulfonamide drugs. Merthiolate should never be given in amounts exceeding 0.15 gram per 100 lbs. of body weight; nor more frequently than once in 10 days. This drug should not be used if there is evidence of active hemorrhagic nephritis.

In the use of the sulfonamide drugs an effort was made to maintain the usually accepted levels of concentration in the blood. Two patients have been treated with neoarsphenamine.

Of the 28 cases in this series, seven were of the acute or malignant variety, and 21 of the subacute variety. All the latter were infected by nonhemolytic streptococcus. There were no recoveries in this series (table 1).

TABLE I

Chemotherapy of Bacterial Endocarditis

Acute Bacterial	Drug Used	Result
Pneumococcus X	Sulfapyridine	Autopsy
" I	" + Serum I	"
" XII	" + Serum VII	"
" III	Sod. Sulfapyridine	"
" VIII	Sulfapyridine	No autopsy
" V	Sulfapyridine + Serum V	" "
Gonococcal	Sulfanilamide + Fever	Autopsy Aortic Veg.
"	Sulfapyridine	" " "
Subacute Bacterial		
Streptococcus Non-hem.	Drug Used	
9 patients	Merthiolate	Autopsy
2 "	" + Sulf.	Autopsy
1 "	" + Vaccine	"
3 "	Sulfanilamide	"
3 "	Sulfapyridine	"
1 "	Sulfathiazole	"
1 "	Sulf. + Merth. + Neoarsph.	"
Total Number Treated Cases—28		No Recoveries

There were three patients whose histories deserve special mention. The first illustrates how standard methods instituted under apparently ideal conditions, nevertheless failed to bring about recovery (table 2). The second

TABLE II

Chemotherapy of Bacterial Endocarditis; Special Cases of Bacterial Endocarditis

(1) Male, 27, acute gonococcal arthritis
Sulfanilamide from fourth day enough to give continuous concentration in blood of 10 mg. per 100 c.c.
Negative physical examination of heart by competent examiners.
Positive blood culture on entrance.
Three treatments by hyperthermia (physical)
Cardiac murmurs, appeared and increased.
Autopsy: Aortic gonococcal endocarditis.
Pericarditis.

illustrates the possible cure of endarteritis of the pulmonary artery by merthiolate (table 3). The third, a patient on the service of Dr. W. H. Olmstead in St. Mary's Hospital, illustrates the cure of bacterial endocarditis or endarteritis by successful ligation of a patent ductus arteriosus by Dr. J. M.

TABLE III

Chemotherapy of Bacterial Endocarditis; Special Cases of Bacterial Endocarditis

(2) Male, 14, no history of acute rheumatic fever.
Systolic murmur and thrill, second left i.c.s.
High diastolic pressure
Blood cultures 500, 540, 550 colonies per c.c.
Ligation of patent ductus arteriosus
Sterile blood cultures
Clinical recovery

Mudd. This case will undoubtedly be added to the literature by these workers to take its place with one previously described by Touroff and Vessel (table 4).

TABLE IV

Chemotherapy of Bacterial Endocarditis; Special Cases

(3) Female, aged 23
Onset: Sore throat treated with sulfanilamide
Later, fever and pain in left chest.
Examination: Systolic murmur second i.c.s. left
Blood Cultures: Non-hemolytic strep. 17 times
50 colonies per c.c.
Clinical Diagnosis: Subacute bacterial endocarditis
pulmonic valve (congenital)
Treatment: Merthiolate
Autopsy: Healing pulmonary endarteritis—
mercury poisoning

CONCLUSION

The practitioner in considering the chemotherapy of endocarditis must be sure, first, of the diagnosis. He must then avoid injuring the patient. He must select chemical agents which seem to suit his situation. These are in order of reported successfulness: sulfanilamide; sulfapyridine; sulfanilamide combined with fever physically induced; neoarsphenamine.

A few years more of observation are necessary to determine which of these procedures, if any, is to be uniformly or occasionally successful.

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SPUTUM STUDIES IN PNEUMONIA: THE SELECTION OF THERAPY *

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DURING the past few years the sulfonamide drugs have proved to be so effective that they have largely supplanted serum in the treatment of pneumococcic pneumonia. Some clinicians, however, use both forms of medication either simultaneously in critically ill patients or separately in the event of failure of one agent alone. Because of the known differences in the mode of action of serum and chemotherapy, and because of variations in the severity of different cases, it would seem desirable to individualize specific treatment if some satisfactory criterion was available which would indicate the exact status of each patient. During the past four years we have been studying Wright stained smears of rusty sputum from patients with pneumococcic pneumonia in an effort to obtain information concerning the pneumonic process in the lungs of individual cases. Several observations made during this study which are of particular interest are summarized below. For the technic and detailed results the reader is referred to the original publications.[1, 2, 3, 4, 5, 6]

It was noted that the number of extracellular encapsulated pneumococci in rusty or bloody sputum constituted a reliable index of the severity of the pneumonic process. This observation has made possible an accurate estimate of the prognosis in each case. A definite correlation was obtained between the number of pneumococci per oil immersion field in smears of the sputum and those clinical factors which are usually regarded as true indices of the severity of the infection. Thus, as the number of pneumococci per field increased a corresponding rise in mortality rate, incidence of bacteremia, leukopenia and multiple lobe involvement also occurred. If the sputum count exceeded 50 per field, the prognosis was usually grave regardless of what form of therapy was administered.

Examination of sputum has also revealed the difference in the mode of action of serum and chemotherapy as seen in human patients. Within 8 to 36 hours after the intravenous injection of specific horse or rabbit serum the pneumococci in the sputum were found to be agglutinated, and in many cases an increased phagocytosis of the organisms was demonstrable. The number of pneumococci per field, however, decreased gradually in most instances so that by the time the sputum lost its rusty character only a few

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were present. Occasionally specimens of sputum from patients who had not yet received therapy contained pneumococci which were already agglutinated. In these cases it was believed that the spontaneous clumping was indicative of a developing active immunity on the part of the patient himself.* It was also observed that when serum was given to patients with large numbers of pneumococci in the sputum the induction of agglutination was difficult and in some cases a progressive increase in number of pneumococci occurred even in the presence of clumping and phagocytosis. Chemotherapy, on the other hand, usually accomplished that which serum often failed to do. Within 12 to 36 hours after the administration of sulfanilamide, sulfapyridine, or sulfathiazole the number of pneumococci per field in the sputum decreased rapidly. This effect was independent of the agglutination and phagocytosis associated with active or passive immunity. Occasional patients were encountered who failed to show a decrease in the

TABLE I

Method of Selecting Therapy

Pneumococci per Field	Day of Illness	Sputum Clumping	Treatment
10 or less	4 or more	−	No specific treatment
	Any	+	
10 or less	3 or less	−	Antipneumococcic serum
11 to 50	Any	+ or −	Sulfapyridine or sulfathiazole
51 or more	Any	+ or −	Chemo- plus serum therapy

number of pneumococci, but the majority of those treated with the three drugs responded with a typical bacteriostatic effect in the sputum. "Drug fastness" as judged by the return of the pneumococci to the sputum following an initial decrease was observed in 17 per cent of the patients treated with sulfanilamide, whereas the same phenomenon occurred in 6 per cent of those given sulfapyridine and in only 2 per cent of those treated with sulfathiazole.†

If the above observations were correct it ought to be possible to conduct a therapeutic experiment in which the patients are grouped according to prognosis on admission to the hospital and an adequate form of therapy selected for each patient by means of the sputum examination. We have accordingly treated 270 roentgenographically proved cases of types I, II, IV, V, VII, and VIII pneumonia in which the sole criteria for the selection of therapy were the sputum findings and clinical data listed in table 1. In such an experiment the lowest mortality rate would be expected in those cases which received serum or no specific treatment, whereas the highest mortality

* Studies in progress at the present time indicate that spontaneous clumping of pneumococci in the sputum is due to the production of agglutinins by the host.

† Evidence is now available which indicates that these drug fast strains are able to grow in concentrations of sulfapyridine and sulfathiazole exceeding those found in the patients' blood during therapy.

would occur in those patients who were given sulfonamide drugs or combined therapy. The important factors of age, pneumococcus type, bacteremia, leukopenia, and the degree of pulmonary involvement were not considered. Subsequent specimens of sputum were obtained at intervals of 12 hours to determine whether or not a therapeutic effect had been obtained, and the appropriate treatment was instituted if the number of pneumococci per field increased. Serum therapy was discontinued when clumps of pneumococci appeared in the sputum.[3] During the past year we have also successfully controlled chemotherapy dosage by means of the sputum. The results of these observations will be reported in future communications.

Results

In the group of 48 patients who received no form of specific therapy there were none in whom the blood culture was positive and only a few who had total leukocyte counts below 10,000 or who had more than one lobe of the lungs involved. All of these cases, on the basis of the method of selection used, showed 10 or less pneumococci per oil immersion field throughout their illness (table 2). Specific therapy was withheld in these patients

Table II

No Specific Therapy

Type	Cases	Bacteremia	Leukopenia	Multiple Lobe	Expired
I	18	0	2	1	0
II	4	0	0	1	0
IV	1	0	1	0	0
V	5	0	0	1	0
VII	8	0	1	2	0
VIII	12	0	0	1	0
Total	48	0	4	6	0
Per cent		0%	8%	13%	0%

because it was considered that either adequate immunity was present or the infection was mild enough to be kept in check by the natural defenses of the patients themselves. Although the clinical course in many of these cases was not dramatic, they all recovered satisfactorily from their illness.

In table 3 are included 70 patients who had been ill less than four days but who showed the sputum findings of a relatively mild infection (10 or less pneumococci per field). Since these patients had not been ill long enough to develop an active immunity, passive therapy in the form of specific serum was considered logical in order to prevent the development of a more serious pneumonia. It is interesting to note that although the bacteremic incidence in this group was 17 per cent and although the average dosage of serum for each patient was only 35,000 units, an amount usually considered insignificant in either bacteremic or non-bacteremic cases, there

were no deaths in the series. It is likely that many of these patients would have recovered without any form of specific therapy and probably all would have responded well to sulfapyridine or sulfathiazole. We considered, therefore, that the 118 patients who were not treated or given small doses of serum would have recovered with any form of therapy.

TABLE III

Serum Therapy

Type	Cases	Bacteremia	Leukopenia	Multiple Lobe	Expired	Average Serum Thousand Units
I	16	1	1	1	0	35
II	14	2	0	1	0	40
IV	1	0	0	0	0	40
V	6	2	0	0	0	34
VII	19	4	1	7	0	30
VIII	14	3	2	3	0	30
Total	70	12	4	12	0	35
Per cent		17%	6%	17%	0%	

As previously indicated, chemotherapy was reserved for the group of moderately and severely ill patients (11 to 50 pneumococci per field) who, in the past, had responded poorly or not at all to treatment with serum. The status of the immune mechanism was not considered because of its relative inefficiency in patients with large numbers of pneumococci in the sputum. The institution of an efficient antibacterial therapy was deemed necessary in order to reduce the number of organisms in the pneumonic exudate as quickly as possible. In 114 patients given chemotherapy alone (table

TABLE IV

Chemotherapy

Type	Therapy	Cases	Bacteremia	Leukopenia	Multiple Lobe	Expired
I	Pyridine	14	4	2	6	0
	Thiazole	24	7	1	9	3
II	Pyridine	10	6	2	4	0
	Thiazole	7	4	2	4	0
IV	Pyridine	2	0	1	2	0
	Thiazole	10	3	2	2	0
V	Pyridine	1	0	0	1	0
	Thiazole	7	4	0	3	0
VII	Pyridine	12	5	1	8	2
	Thiazole	11	5	4	8	0
VIII	Pyridine	10	4	3	4	1
	Thiazole	6	3	2	2	1
Total		114	45	20	53	7
Per cent			40%	17%	46%	6%

4) it should be noted that the bacteremic incidence and multiple lobe involvement were significantly increased over those found in the preceding two groups. However, the ultimate fatality rate of only 6 per cent in the presence of a 40 per cent bacteremic incidence would seem fully to justify the choice of therapy. The data also represent additional evidence for the

TABLE V

Serum Plus Chemotherapy

Type	Therapy	Cases	Bacteremia	Leukopenia	Multiple Lobe	Expired	Average Serum Thousand Units
I	Pyridine	3	3	1	3	3	350
	Thiazole	3	3	1	2	1	
II	Pyridine	2	1	2	2	2	380
	Thiazole	5	4	5	5	3	
IV	Thiazole	1	1	1	1	1	100
V	Thiazole	2	2	1	2	1	300
VII	Pyridine	3	1	1	1	0	370
	Thiazole	4	4	3	4	2	
VIII	Thiazole	1	0	0	1	1	440
Total		24	19	15	21	14	323
Per cent			79%	63%	88%	58%	

therapeutic efficiency of sulfapyridine and sulfathiazole in moderately to severely ill patients.

We considered that those patients with sputum counts exceeding 50 per oil immersion field were potentially overwhelmed by their infection. Although only 24 patients were placed in the above category, the majority of them showed blood stream invasion, low total leukocyte counts, and two

TABLE VI

Miscellaneous Cases

Original Rx	Cases	Bacteremia	Leukopenia	Multiple Lobe	Expired	Additional Reasons for	
						Rx	Rx
Serum	5	1	0	2	1	Chemo	Sputum Count
Serum	2	1	0	1	1	Chemo	Pericarditis
Serum	1	0	0	0	0	Chemo	Phlebitis
Chemo	1	1	1	1	0	Serum	Hemolytic anemia
Chemo	1	1	0	0	0	Serum	Pericarditis
Pyridine	1	1	1	1	0	Pyridine	Enthusiastic interne
Pyridine	2	1	0	2	0	Thiazole	Pneumococci pyridine fast
None	1	0	0	0	0	Chemo	Unexplained fever
Total	14	6	2	7	2		

or more lobes involved during their illness. They were given, accordingly, large doses of serum in addition to chemotherapy.* In spite of the intensive treatment the mortality rate (58 per cent) was considerably higher than that in the preceding three groups of cases.

Fourteen cases were placed in a miscellaneous group presented in table 6. Five patients received initial serum therapy, but in subsequent specimens of sputum the number of pneumococci had increased to more than 10 per field. Serum was, therefore, discontinued and chemotherapy substituted in its place. The forms of therapy given to the remaining nine patients and the reasons for the additional treatment are recorded in the last column of table 6.

Discussion

A total of 270 cases was studied in which the bacteremic incidence was 30 per cent and the mortality rate was 9 per cent. The figures have not been corrected and, therefore, include all deaths from pneumonia and its complications irrespective of the duration of illness and the period of hospitalization. Approximately 50 per cent of the patients were considered as potential survivors under any form of treatment and only 10 per cent of them were characterized as potential deaths under any form of treatment. It should be pointed out that we did not believe that all patients received the most effective form of therapy. This is especially true in the group of 118 cases which were given either serum or no form of specific therapy. While the ultimate outcome was favorable, their clinical course, as indicated by temperature and pulse response, was frequently not dramatic. On the other hand serum plus chemotherapy was deemed necessary in only 10 per cent of the percentage studied. However, the results of combined therapy cannot be properly evaluated until they are compared with those obtained in a similar group of selected cases treated with sulfonamide drugs above. In the final analysis of the above and additional cases the clinical factors will be considered in detail.

Most clinical trials of therapeutic agents in pneumonia have been based primarily on the method of alternate case selection. In order to obtain significant results large numbers of patients must necessarily be studied. The method fails to take into consideration those cases which would survive under any form of therapy and discards the overwhelmingly ill patients who expire shortly after admission to the hospital. The classification of cases into prognosis groups by means of sputum examination appears to be a method of case selection which would permit a true comparison of the efficacy of various therapeutic agents. The results of the therapeutic experiment which have been presented strongly support this concept. We also believe that the sputum findings afford a method of recognizing severely ill patients on admission to the hospital so that combined therapy may be in-

* Most of the patients in this group received the sodium salt of sulfapyridine and sulfathiazole intravenously.

stituted immediately. Although such patients represent only a small percentage of the total cases of pneumonia, they, nevertheless, are responsible for the majority of fatal terminations. In addition to the above, sputum examinations are of value in determining whether or not chemotherapy is producing the desired bacteriostatic effect and in the detection of cases in which the pneumococci have become resistant to the drugs. We are also utilizing the sputum as a method of controlling the dosage and period of administration of both serum and chemotherapy. The results of the above studies will be presented in future communications.

Summary

In a series of 270 typed cases of pneumococcic pneumonia the therapy for each patient was selected by means of sputum examination. The results which were obtained support the concept that the sputum findings may be used as a reliable aid in prognosis and also as a method of individualizing therapy for each patient.

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THE MEDICAL ASPECT OF ANKYLOSING SPONDYLITIS (MARIE–STRÜMPELL) *

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Introduction

Lying between the fields of internal medicine and the specialties is a borderland into which the patient may stray and be lost to adequate diagnosis and treatment. It is here that the larger number of medical mistakes are made. In this connection we, as internists, have been impressed by the frequency with which Marie-Strümpell, or ankylosing, spondylitis is unrecognized and mistakenly labelled. We are, furthermore, convinced of the importance of considering this somewhat rare malady in the diagnosis of any painful state of the torso or extremities. With a clear picture of the disease in mind and with ordinary laboratory and roentgenologic facilities at hand, its recognition is not difficult. Our experience suggests the desirability of presenting Marie-Strümpell arthritis less as an orthopedic and more as a medical problem, especially a diagnostic one. Such is the purpose of this paper.

Historical Note

This syndrome has been established by the studies of a very few men. If we regard priority, the name of Von Bechterew should be attached to the disease, since this observer published the initial description in 1892. Strümpell in 1897 and Marie in 1898 followed with reports of the characteristic clinical picture now bearing their names. It is of interest that Von Bechterew emphasized the disturbances of innervation, the pain and the paresthesias, hyperesthesias, paresis and atrophy of muscles, and the tenderness on percussion, many of these being among the rarer manifestations of the disease. Strümpell was the first to note the abnormal straightness of the spine. In contrast to Von Bechterew he was impressed by the slight amount or absence of pain. Bachman, who first stressed the involvement of the sacroiliac joints, found 60 examples of ankylosing spondylitis in an examination of 2,561 spines. This is a higher proportion than any other observer has reported. In a study of 98 cases Fischer found involvement of the lumbar spine in 96 per cent, of the dorsal spine in 89 per cent, and of the cervical spine in 54 per cent, while the sacroiliac joints were implicated in 79 per cent. In 29 per cent of the same series there were associated changes in the smaller joints of the extremities characteristic of rheumatoid arthritis. A classic contribution is Schmorl's necropsy study of 10,000 spines, among which number but eight examples of ankylosing spondylitis

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were found. This well illustrates the rarity of the condition, a finding in accord with general clinical experience.

The English literature of ankylosing spondylitis is meager. Elliott in 1905 described five cases, four of which followed gonorrheal infection. Buckley, who first noted the characteristic increase in the sedimentation rate, cited 60 cases, only six of which were women. Joseph Miller discusses briefly the importance of Marie-Strümpell arthritis in the diagnosis of chronic rheumatic disease of the spine. With these exceptions the disease has been passed by in silence, especially by the internist.

Clinical Features

This disease has attracted our special attention during the past five years. During this period, in an office practice, we have recognized but 10 cases. We estimate this as about 0.2 per cent of all new patients. The rarity of the malady is, therefore, apparent. We have found that ankylosing spondylitis is about as common as gout in ambulant private patients in New York City. The important diagnostic features may be discussed.

In our experience the disease is most common in males in the fourth decade. The onset is insidious and the progress slow. There are, however, acute cases which are more easily recognized. The dominant symptom is pain. The feature of this pain is its variability and the vagueness with which even the most intelligent patient describes it despite its severity. In the same individual the pain varies in site, degree and character from one phase of the disease to another. It may be in the back, the hip or shoulder girdles or in the distribution of the sciatic nerve. Although it may be continuous, it does not maintain a constant pitch of intensity. Characteristically it is worse during the last hours of the night. Often the patient is awakened about four a.m. and passes the rest of his time in bed in discomfort. After the patient has had a hot bath and has been about for a few hours, the pain gradually subsides. Usually the least amount of pain is experienced during the afternoon and evening. Any sudden or violent movement such as sneezing or coughing greatly increases the pain. In rare cases pain is not a prominent feature and is reported only after cross-questioning. The great variability of the pain needs emphasis. Pain about the shoulder girdle often suggests that of a subdeltoid bursitis; that about the hip a *malum coxae senilis;* again, a sciatica. Root pains may suggest pleurisy, intercostal neuritis, renal colic, or even a surgical abdomen. Sensory changes, usually hyperesthesia, are rarely impressive. Muscular weakness is common, muscular atrophy occasional.

In the majority of cases the onset is insidious with exacerbations and remissions but the disease may begin acutely with agonizing sciatic or lumbar pain suggesting a mechanical rather than an infectious etiology.

Second in importance in symptomatology is stiffness. In this symptom there are two factors: the first, muscle spasm which is the result of pain;

the second, actual organic changes with more or less fixation of the joints. The joints involved are the sacroiliacs, the small posterior intervertebrals, and the costovertebrals. Almost always the sacroiliacs are the first to be affected. This explains the frequency of sciatic pain. The muscles in which spasm is most obvious are the extensors of the spine. Undoubtedly the flexors are affected in like manner since motion in all directions is limited. When the cervical spine is involved, there is inability to rotate the head. This gives a very characteristic movement on attempting to look to the side and backward, since the entire torso turns with the head. The resulting gesture is almost diagnostic. The dorsal and lumbar spine may be more or less rigid so that movements of flexion and rotation are curtailed.

One of the most striking symptoms is rigidity of the thoracic cage. This results from involvement of the costo-vertebral joints and is shown in the lack of expansion of the chest on inspiration. Respiration is entirely diaphragmatic. It is interesting that the ribs tend to be fixed in an expiratory rather than an inspiratory position, the opposite of that seen in emphysema. To some extent these changes account for the curious and characteristic posture assumed by these patients. The head is carried forward, the chin depressed. With this is a moderate dorsal kyphosis and a flattening of the anterior chest. A lowered vital capacity results with lessened bellows effect of the lungs and consequent disadvantage to the circulation. A striking effect of the loss of flexibility of the lumbar spine is a lessening of the normal lumbar lordotic curve with a flattening of the lower back. To this muscular spasm contributes. When, as is frequently the case, the shoulder and hip joints are involved, stiffness can be demonstrated here. It is of interest that the process rarely affects any of the smaller joints of the extremities. In most cases the disease begins in the lumbar spine and extends upward but occasionally the cervical spine is first involved. Of the local manifestations tenderness is of considerable importance diagnostically. This is most common over the sacroiliac joints and the spinous processes. It is not always present. In some cases characteristic tenderness may be elicited by percussion over the spine or pelvic bones rather than by pressure.

Certain general symptoms occur in all but the most recent cases. There is loss of weight, of strength and of general muscle tone. In many cases the loss of weight is extreme, amounting to 40 or 50 pounds within a year. In such the question of malignancy, tuberculosis or other wasting disorder naturally is raised. Fever may be absent, or slight, rarely exceeding 101° F. The pulse is rapid as a rule, averaging 90 to 100 per minute. There is occasional anorexia. The mental aspect of these patients deserves notice. They seldom smile. There is a uniform dejection and depression. It is difficult to be sure that this is not other than one might expect in any chronic painful disease. To us, however, it has seemed to have certain features that become characteristic when observed in association with the typical attitude and posture of these patients. Rheumatic nodules are never

found. An occasional case will exhibit an endocarditis or an iritis which cannot be distinguished from those of rheumatic fever. Such findings imply a relationship between rheumatic fever and Marie-Strümpell arthritis.

Roentgenographic Findings

These are diagnostic. The initial finding is a haziness of the sacroiliac joints with an increased bone production along the joint margins which eventually leads to bony fusion. In a later phase a similar process involves the posterior intervertebral joints of a portion or of the entire spine. In the most advanced stage there is a calcification of the anterior and lateral ligaments of the spine producing the typical bamboo appearance which is pathognomonic. A general decalcification of all bones may be seen, often quite early in the disease. It is important that the clinician remember that the roentgen-ray changes characteristic of the malady may be late in appearance and that pain, stiffness and other symptoms often precede roentgenologic findings by months or years.

Laboratory Findings

The laboratory is of very little aid in the diagnosis. The most constant finding is an elevated sedimentation rate. Typically, this varies between 30 and 80 mm. In contrast to the finding in rheumatoid arthritis, the streptococcus agglutinins are not increased. Secondary anemia is frequent. There are no characteristic changes in the leukocytes.

Case Reports

Case 1. A male of 20 years who had suffered gradual onset of pain and stiffness in the distribution of the right sciatic nerve over a period of one year. Eventually the pain became severe enough to interfere seriously with the patient's rest, especially in the early morning hours. The only positive physical findings were a slight atrophy of the right thigh and decreased deep reflexes in that extremity. There was no stiffness of the spine. The sedimentation rate was 34 mm. The roentgenograms of the spine and hips were negative. A definite diagnosis was not made. With salicylates and rest there was apparent recovery. The patient was seen three years later, again complaining of the former symptoms with the addition of pain and slight stiffness in the lower back. Roentgen-ray study at this time was negative. The sacroiliac joints revealed no significant changes. An orthopedic consultant was of the opinion that the sciatica was due to an acute lumbo-sacral angle. A spinal fusion was advised. This recommendation was not followed. Again improvement followed medical treatment. Five years after onset the pain became so severe that the last half of the night was spent in serious discomfort. At this time examination showed definite stiffness in the lumbar and cervical spine, and for the first time the roentgenograms showed haziness in the sacroiliac joints. The rest of the spine was negative. The sedimentation rate was 27 mm. The diagnosis of Marie-Strümpell spondylitis was then made, six and a half years after the onset. The subsequent course has validated this diagnosis. A course of chrysotherapy was without benefit. Radio-therapy and general measures, including rest, have been followed by moderate improvement.

Case 2. A man of 53 years who complained of dyspnea and of recurrent attacks of pain and stiffness in the lower back. Occasionally these attacks were quite severe and associated with pain and stiffness in the hips and shoulders. Physical examination revealed the murmurs of mitral stenosis and of aortic insufficiency. These had been reported during the past 25 years. Stiffness of the lumbar and dorsal spine was present. Roentgenograms showed calcification of the lateral ligaments of the dorsal spine with haziness of the posterior intervertebral joints. The sacroiliac articulations were relatively normal. The sedimentation rate was 22 mm. in one hour.

Case 3. A woman of 55 years who complained of severe but intermittent low back pain of one month's duration following an unusual strain in lifting a heavy object. Similar though milder attacks had been suffered in the past. The physical examination revealed a markedly spastic and rigid spine painful on the least motion. The severity of the symptoms and the acuteness of the onset suggested either an osteomyelitis, neoplasm or serious mechanical derangement of the spine. The temperature was 100° F., orally, and the sedimentation rate was 55 mm. Roentgen-rays of the spine made the diagnosis evident in calcification of the lateral ligaments, sacroiliac arthritis and generalized decalcification of all bones.

Case 4. A man of 36 years with a five year history of pains in the thighs, hips and shoulders, of occasional attacks of sciatica, and of loss of energy and strength. The onset was acute, with fever reaching 102° F., and lasting about two weeks. Since this, symptoms have been more or less continuous, but of varying severity; never incapacitating. The physical examination disclosed definite limitation of motion in both the lumbar and cervical spine. Roentgenologically there was generalized decalcification of bone, calcification of the anterior longitudinal ligament in the cervical region and haziness of the sacroiliac joints. A sedimentation rate was not recorded in this case.

Case 5. A man of 38 complained of waking in the early hours of the morning with stiffness and pain in the mid-back and shoulders. This was relieved by aspirin and by pacing the floor, after which he was able to return to sleep in from one-half hour to two hours. These symptoms, which had been present for 10 years, were variously ascribed to spastic colon, lumbago and sciatica. A chance finding of hematuria on one occasion had raised the question of renal pathology, but repeated cystoscopic and other studies had been negative. The physical examination revealed only stiffness of the lumbar spine with pain on attempting flexion. The sedimentation rate was 10 mm. Roentgen-rays of the spine showed destruction of the right sacroiliac joint with marginal sclerosis, obliteration of the posterior intervertebral joints of the lumbar spine, and generalized decalcification. The subsequent course has been unsatisfactory because of increasing pain and stiffness in the spine.

Case 6. A man of 32 who complained of stiff and sore back muscles with occasional attacks of sciatica of six years' duration. He noted that sneezing particularly provoked severe pains in the back and chest. Sleep was disturbed by the pain during the early morning hours. Recently there had been a decrease in chest expansion, and a rigidity of the spine. The sedimentation rate was 40 mm. Roentgen-rays showed complete fusion of the sacroiliac joints and obliteration of the small posterior intervertebral joints of the thoracic and lumbar vertebrae. It is interesting that this patient's father also had a poker spine.

Case 7. A man of 50 who gave a history of arthritis of the spine of 17 years' duration associated with recurrent attacks of severe iritis. The arthritis and iritis began at the same time and a flare-up of the one was always associated with increased activity of the other. In recent years the neck had also become stiff so that the entire spine was a rigid fixed unit. Due to fixation of the chest in the expiratory position dyspnea had been present on exertion. Physical examination disclosed a classical poker spine and many adhesions of the iris. Roentgenograms disclosed a bamboo

spine with complete replacement of the sacroiliac joint spaces by bone. The sedimentation rate was 80 mm. in one hour.

Case 8. A woman of 32, with a history of 15 years of recurring attacks of low back and left sciatic pain. These attacks occurred without warning and were severe and crippling. The patient was found to be in severe pain with back held rigid, any motion causing agonizing paroxysms. The lumbar muscles were board-like in their rigidity. The sedimentation rate was 30 mm. in one hour. Roentgen-rays of the spine were negative save for a moderately advanced sacroiliac arthritis, and generalized osseous decalcification. Radio-therapy gave prompt relief.

Case 9. A man of 36 years with a history similar to that of case 8. For 10 years he had noted pain and stiffness in the lower back, with periods of exacerbation and remission. There had been some weight loss. During this time no definite diagnosis had been made. Several observers had suggested that some obscure systemic disease might be responsible. Physical examination showed moderate limitation of motion in the lumbar spine. The sedimentation rate was 30 mm. in one hour. Roentgen-rays revealed definite blurring of the sacroiliac joints and of the posterior intervertebral joints of the lumbar spine in addition to a generalized decalcification of all bones.

Case 10. Spondylitis began at the age of 30 and was very severe, painful and crippling. The accepted diagnosis was Pott's disease. A plaster jacket was worn without relief. Finally a spinal fusion was done. After this there were five years of disability because of prostration and active symptoms. For several years after this pain continued; later it gradually disappeared. The patient on examination presented the characteristic aspect of ankylosing spondylitis in its quiescent end stage with poker spine and lack of thoracic respiration. Roentgen-rays showed operative fusion of the lower lumbar vertebrae and spondylitic fusion of the thoracic vertebrae. The patient felt that the course of his disease was not altered by the spinal fusion. He was convinced that the surgical procedure subjected him to much needless suffering and inconvenience.

Treatment

The disease should be managed as a chronic infection. A regimen such as one might enforce in tuberculosis in a latent stage is applicable in the treatment of ankylosing spondylitis. Fatigue is to be avoided; nervous stress and strain reduced to a minimum; long rest periods prescribed. If the patient must work, week-ends in bed are a desirable compromise. A long stay in the tropics especially in the cold months is most helpful. The patient's nutrition should be improved by a high caloric diet supplemented by ample vitamins. Large amounts of vitamin D are especially desirable. Crude cod liver oil, if tolerated, should be given in large amounts. If anemia is present vitamin B in addition to iron is indicated. Salicylates, aspirin or, temporarily, codeine are useful to control the pain. Prolonged hot baths, turpentine stupes, and diathermy are further measures. Pains should be taken to preserve as erect a posture as possible because of the inevitable fixation of the spinal joints as the disease progresses. The patient should sleep on a hard bed with a sheet of plywood between mattress and springs, if possible without a pillow. A plaster jacket in which to sleep and a leather jacket worn as a brace in some instances are valuable measures. On the whole chrysotherapy has been valueless in this syndrome.

Prognosis

The disease rarely shortens life. Gradually after years the acute symptoms subside and the patients are left with the end stage structural changes in the affected joints. These cause varying degrees of disability from stiffness. The patients seldom stir with alacrity. They continue to show the attitudes and patterns of movement so characteristic of the disease. Pain is minimal or absent. In the average case one finds a satisfactory adjustment to life on a somewhat lowered level of activity.

Summary

In summarizing the experience of internists in the diagnosis of ankylosing spondylitis we would emphasize the following points.

The disease is rare. Probably the majority of cases are undiagnosed. Many are wrongly diagnosed and wrongly treated. Perhaps the greatest error is the subjection of many of the victims of this disease to spinal fusion —a measure as futile as it is severe. As in so many other situations, diagnosis depends largely upon keeping the syndrome in mind when the problem of spinal disease comes up for consideration.

The penchant of ankylosing spondylitis for the male in the third to the fifth decade, the great variability of the symptoms, the lack of definition in localizing and describing the pain, its intermittent character, the peculiar attitudes and movements of the patient, the immobility of the thoracic cage, the slight or absent fever, the stiffness of the spine and the abnormal straightening of its lumbar segment, the roentgenographic findings, the elevated sedimentation rate, the occasional involvement of the smaller joints of the extremities and the rarer event of an endocarditis of the rheumatic type, all are important diagnostically. If the physician is alert to this picture, confusion with other pathologic states is unlikely. Naturally one must differentiate other diseases of the spine, among which one may mention late rickets, Pott's disease, prolapse of a nucleus pulposus, osteoarthritis, malignant disease of the bone or cord, sciatic neuritis, Paget's disease and osteomyelitis.

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RHEUMATISM AND ARTHRITIS

REVIEW OF AMERICAN AND ENGLISH LITERATURE FOR 1940

(Eighth Rheumatism Review) *

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CONTENTS

General incidence of rheumatic diseases 1003
Classification of diseases of joints and related structures 1003
Diseases of joints related primarily to trauma 1003
Gonorrheal arthritis and gonorrheal rheumatism 1005
Tuberculous arthritis 1009
Pneumococcal arthritis 1011
Syphilitic arthritis and synovitis; Charcot (tabetic) joints 1011
Brucellosis: undulant (Malta) fever 1012
Suppurative arthritis 1014
Rarer forms of specific arthritis 1015
Rheumatic fever 1016
Rheumatoid (infectious, atrophic) arthritis 1026
Still's disease 1050
Osteoarthritis: degenerative joint disease 1051
Backache and sciatica 1055
Rheumatoid (ankylosing) spondylitis 1060
Osteo-arthritic (hypertrophic) spondylitis 1062
Gout and gouty arthritis 1062
Psoriatic arthritis 1066
Hemophilic arthritis 1067
Endocrine arthritis 1067
Miscellaneous types of joint disease 1068
Diseases of bursa 1071
Diseases about the shoulder joint: the painful shoulder 1071
Diseases of muscles and fibrous tissues 1073
Fibrositis 1073
Miscellaneous conditions 1075
Other studies on joints and related tissues 1076
Rheumatism and the war 1079
Campaign against rheumatism 1081

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General Incidence of Rheumatic Diseases: Social and Economic Importance

The appalling morbidity and invalidism produced by rheumatic diseases in the United States and abroad were again emphasized by Snyder and others.[123, 435, 448] More than 320,000 otherwise able persons in the United States are rendered unemployable for an entire year by these disorders; the greatest incidence occurs among persons without maintenance incomes.[448] Calling arthritis "a neglected disease," Snyder urged physicians and laity to appreciate fully its sociologic and economic importance and to provide adequate facilities for the care of its many victims.

New data from the National Health Survey[66, 67] indicated that rheumatic diseases were the sixth greatest cause of disability among persons surveyed. The rheumatic diseases ranked third among those which disabled persons for a year or more. The incidence of rheumatic diseases was related to the annual family income; it was 3.5 times as great among persons on relief and twice as great among those whose family income was less than $1,000 as among those who had a family income of $3,000 or more.[67]

Definition of "Rheumatism" and the "Rheumatic Diseases"

No new definitions of rheumatism and rheumatic diseases appeared. Admittedly a poor term, "rheumatism" still remains the best word by which to refer to that great group of diseases, the "rheumatic diseases" characterized largely by pain in ligaments, muscles or joints.[524]

Classification of Diseases of Joints and Related Structures

Differentiation of the rheumatic diseases was considered the first requisite for their accurate clinical investigation and therapy.[448, 503, 524] Remarks on various classifications were made.[435, 448, 464, 503, 524]

At its June, 1941, meeting the American Rheumatism Association adopted the following provisional classification: (1) specific infectious arthritis (organism known); (2) arthritis of rheumatic fever; (3) rheumatoid arthritis (synonyms: atrophic, proliferative and chronic nonspecific infectious arthritis, Still's disease, Marie-Strümpell spondylitis); (4) osteoarthritis (synonyms: degenerative joint disease, hypertrophic, senescent arthritis); (5) arthritis of immediate traumatic origin; (6) arthritis of gout; (7) arthritis of neuropathic origin (Charcot's joint); (8) neoplasms of joints; (9) miscellaneous forms (or arthritis associated with other diseases).

Diseases of Joints Related Primarily to Trauma

Traumatic Arthritis and Synovitis. Of 483 injuries of knees sustained in sports 203 resulted in ligamentous strains, 145 in joint contusions, 78 in muscular contusions, 43 in internal derangements, eight in bursal contusions and six in superficial contusions.[574] Differential diagnosis is often difficult; prognosis should be reserved until 24 or more hours after injury.

Sprains and Strains. Ligamentous sprains produce tears and hemorrhages in tissues and must be followed by absorption of hematoma and repair of tissue. Treatment should be aimed toward minimizing the hematoma.[574] Thorndike recommended the immediate application of ice water, then the use of a compression sponge rubber bandage and rest. Convalescent treatment consists of heat, gentle massage and early weight bearing, the joint being supported by a compression bandage.

Internal Derangements of Knees. The mechanism of injury is similar in most cases: internal torsion of femur on tibia with the knee in partial flexion. In the cases of Ferguson and Thompson 52 per cent of such injuries occurred in competitive sports; football accounted for 29 per cent. Symptoms of the various internal derangements are similar; diagnosis cannot always be established definitely before operation.[602] Aspiration may help to determine the amount of intra-articular injury: hemarthrosis indicates a tear of some intra-articular structure. Aspiration and "fixation with function" should constitute preliminary treatment. Recurrence of disability, especially locking, effusion and instability, warrants operative intervention.[188, 260, 602] If the internal derangement is of long standing, secondary osteo-arthritis may be expected; such changes were found in 47 per cent of Wilmoth's cases.

The commonest internal derangement of the knee is damage to the internal semilunar cartilage. Of 121 patients who were operated on for this condition 105 were found to have the internal semilunar cartilage involved alone; 12, the lateral cartilage alone, and four, both the internal and lateral cartilages.[602] Manipulations under anesthesia, with reduction of the dislocated cartilage, were followed by recurrence in every case of Ferguson and Thompson who advised early surgical intervention in any knee with true locking. But Henderson did not recommend operation until locking had occurred several times: his surgical treatment resulted in "complete relief" in 77 per cent of cases, "improvement" in 15 per cent.

Hypertrophy of infrapatellar fat pad without injury to cartilage comprised 16 per cent of the internal derangements seen by Ferguson and Thompson. Symptoms were pain, effusion, limitation and instability. Preoperative diagnosis was usually incorrect. Excision of the fat pad gave relief in 75 per cent of cases.

Derangements from osteocartilaginous loose bodies may be due to osteochondritis dissecans, osteochondromatosis or osteo-arthritis.[260] Osteochondritis dissecans was thought to be caused by the blocking of an end artery with consequent aseptic necrosis of a portion of bone and cartilage and the subsequent breaking off of a wandering osteocartilaginous fragment. Osteochondromatosis was considered to be a benign neoplastic process with the bodies originating in synovial membrane. Both conditions occur in young persons; operative results are excellent.[260] Surgical removal of osteocartilaginous bodies due to osteo-arthritis in elderly persons was not advised unless troublesome locking occurs.

Penetrating Wounds of Joints. Early excision of damaged tissue, removal of clots and fluid and irrigation of joint space (if contaminated) with pure ether were recommended by Ferguson and Dangerfield for perforating wounds of the knee. Air aspirated into a joint through a superficial wound may erroneously suggest a gas bacillus infection.[583] Even though not infected, foreign bodies (bullet, glass, needle) if not removed from joints may

cause progressive degenerative arthritis: Key reported six such cases. Foreign bodies in or near joints should be removed before degenerative changes result, except in intervertebral joints where fusion is asymptomatic.

Gonorrheal Arthritis and Gonorrheal "Rheumatism"

Incidence. There is no evidence that the incidence of gonorrhea has been materially reduced since the introduction of the sulfonamide compounds. But some believe that complications of the disease have diminished. At one hospital the yearly incidence of gonorrheal arthritis has been more than halved.[539]

Among women with gonorrhea seen by Salberg, Brunet and Koch[76, 487] gonorrheal arthritis developed in only 0.5 to 0.8 per cent. Carpenter and Westphal studied the problem of the gonococcus carrier. To eliminate the possibility of reinfection, they studied male inmates of a penal institution (Attica, New York) where supervision is rigid and the average sentence five years. Among 1,061 inmates examined (937 white, 124 colored) 35 per cent of the whites and 50 per cent of the negroes gave a history of gonorrhea. Pelvic organs were carefully examined; smears and cultures were prepared from urethral exudate, prostatic secretion, urinary sediment and anal discharge. No acute infections were noted. Eleven carriers were found, all white. Three had symptoms and eight had signs of the disease. From each carrier, *Neisseria gonorrheae* was isolated in culture from varying sources. Smears were negative except in one case. The longest proved carrier state (measured only from time of prison entry) was seven years and two months; others were weeks to one, two, and three years. Extragenital and homosexual infection seemed to be ruled out by the physical surroundings and use of individual toilets. The 11 carriers represented 2.8 per cent of men with a positive history and 1 per cent of the inmates examined. Seven of the 11 carriers continued to harbor the gonococcus despite long, vigorous treatment, including sulfanilamide.

[The paper is excellent and reëmphasizes the value of cultural methods. It shows conclusively that for years a person can have a low-grade carrier-state, difficult to overcome, also that a focus for the possible development of gonorrheal arthritis can smolder indefinitely.—Ed.]

Clinical Data. Usual features of gonorrheal arthritis were exemplified in reports of about 300 new cases.[25, 122, 141, 143, 202, 438, 487, 539] Proved monarticular gonorrheal arthritis in an infant (three weeks old) was successfully treated with sulfanilamide.[438] The mother had suffered from mild gonorrheal arthritis one week before delivery. Reported cases of gonorrheal arthritis of the newborn were reviewed. Gonorrheal polyarthritis developed in a child eight months old, shortly after it was given blood transfusions from its mother who for nine years had had arthritis, "a sequel to gonorrhea." Gonococci were recovered from the child's synovial fluid but not from the mother's blood.[193]

Keratosis blennorrhagica is a distinct entity characterized by gonorrhea, cutaneous keratosis and polyarthritis. It occurs about once in 5,000 to 7,500 cases of gonorrheal urethritis. Only 93 cases have been collected from the literature. Combes, Dietrich and Cohen added two more cases. The arthropathy usually precedes the skin lesions, and differs from the usual gonorrheal monarthritis in the simultaneous involvement of several

joints, chiefly knees, ankles, wrists and acromioclavicular joints. Pain is severe but redness and periarticular edema are less than in gonorrheal monarthritis or in rheumatoid arthritis. Of all remedies used, fever therapy has given best results. In two cases resistant to the sulfonamides skin and articular lesions rapidly disappeared during the use of the inductotherm.

Diagnosis. No new diagnostic aids were described.

Pathology. No studies on this subject were reported.

Roentgenograms. A feature regarded by an Italian physician as diagnostic in early gonorrheal arthritis was mentioned.[464] [The original articles by Lupo, 1935 to 1939 should be consulted.—Ed.] No new data were contained in two other reports.[194, 529]

Laboratory Data. A well organized, discriminative collection of experimental and clinical data devoted largely to the biology of the gonococcus and its infections was published by the United States Public Health Service.[570] It contains valuable information concerning laboratory procedures discussed later.

1. Identification of Gonococci in Smears. No new technic was proposed.

2. Cultures of Gonococci. Shaw and McAllister recommended washing ascitic fluid agar plates with tetra methyl-p-phenylene diamine hydrochloride, after 48 hours' incubation, to aid in identifying gonococcic colonies. The resulting oxydase reaction immediately turns colonies purple, later deepening to black. These colonies then are stained with Gram's stain, examined and subcultured on appropriate media for identification. [The authors admitted that this reaction is not specific for gonococci; *Escherichia coli, Bacillus coli* and *Bacillus subtilis* show the same but less intense staining.—Ed.] Dienes[161] observed that certain cultures of gonococci, before disintegrating, swell up into large, deeply stained, spherical bodies. If these cultures are kept one to two days at 25° C., a slight secondary growth appears in the agar below the colonies. This growth consists of fine filaments and small granules which disintegrate rapidly. These secondary forms resemble the "L_1 colonies" of *Streptobacillus moniliformis.* Attempts to separate these secondary colonies from the parent organism failed.

[These forms may represent a complex method of degeneration of the gonococcus, or perhaps a filtrable form of the organism exists, which may be carried from focus to joints. The inability to grow these tiny forms separately may fit in with the known fact that it is impossible to culture organisms from some gonorrheal joints.—Ed.]

3. Gonococcal Complement Fixation Tests. DiGioia refined the complement fixation test. Others[25, 31, 141, 143, 202] considered the test useful in diagnosis.

4. Comparative Value of Laboratory Tests. The cultural method is superior to all others in diagnosing gonococcic infections.[96, 186, 446, 570]

The Treatment of Gonorrheal Arthritis and Gonorrhea

The literature of 1940 confirmed previous reports[5, 6, 7] that chemotherapy is best for gonorrhea and its complications. Some physicians claimed a greater percentage of cures from the use of local therapy plus a sulfonamide compound; a few preferred hyperpyrexia plus chemotherapy.

It is impossible to evaluate the respective merits of various treatments, because most investigators do not require rigid criteria of cure. Only a few make cultures; most workers depend on smears; some are content with the disappearance of signs and symptoms, or absence of shreds in the "two glass

urine test." If only those reports based on rigid criteria of cure were accepted little could be written about the efficacy of sulfonamide compounds in the treatment of gonorrhea. Other difficulties encountered in making therapeutic evaluations were noted in last year's review. Adherence to a proposed plan devised for the rapid appraisal of chemotherapy in gonorrhea would greatly improve this deplorable situation.[140] It is gratifying to note that most of the worthwhile reports are contributed by the United States Public Health Service.

Before discussing further the treatment of gonorrheal arthritis we shall review briefly the general topic of sulfonamide compounds.

Sulfanilamide and Its Derivatives; General Comment. The present status of chemotherapy,[384, 479] the relative value of sulfonamide compounds,[445] and the nomenclature of modern chemotherapeutic drugs[139, 190] were discussed. New data on the action, and toxic and therapeutic effects of the sulfonamides are presented herein.

1. Mode of Action. From the following case Nesbit concluded that the site of action of sulfapyridine in genital gonococcal infections is in tissues, since the urine was evacuated via the bowel. A patient who had previously had a ureterosigmoidostomy contracted gonorrhea and later prostatitis and epididymitis developed. He was cured in eight days with 23 gm. of sulfapyridine. No new theories as to the mode of action of the sulfonamides were advanced.[479]

2. Absorption, Diffusion and Excretion. Long, Haviland and Edwards noted that sulfathiazole is absorbed and excreted faster than sulfapyridine, but is not as well conjugated by tissues. They concluded that administration of the drug every four hours is necessary to maintain a constant level of sulfathiazole in blood.

3. Toxic Reactions. The acute toxicity of sulfathiazole for mice is a third greater than that of sulfanilamide and about half that of sulfapyridine, sulfathiazole methyl and sulfathiazole phenyl.[367] Long and his colleagues[368] wrote an excellent article on the incidence of toxic reactions among 1,000 patients given sulfanilamide, 297 given sulfapyridine and 271 given sulfathiazole; it was reviewed last year. [They failed to state that liver damage may result from these drugs, with hypoprothrombinemia and bleeding as the first evidence thereof.—Ed.] In one case edema of the uvula developed on the fifth day of sulfanilamide treatment; the patient failed to respond to administration of epinephrine and withdrawal of the drug; amputation of the uvula was performed.[612]

[It is impossible to determine from the data given the exact cause of the edema.—Ed.]

Sulfanilamide in Treatment of Gonorrheal Arthritis. The treatment of gonorrheal arthritis with sulfanilamide was discussed.[25, 31, 75, 76, 141, 143, 202, 241, 438, 539] Sulfanilamide was generally preferred to other compounds. [Some of us prefer sulfathiazole.—Ed.] Results were similar to those reported in the last Review: about 70 to 85 per cent of patients were cured or markedly improved. Culp considered mercurochrome given intravenously, as effective as sulfanilamide.

Sulfapyridine in Treatment of Gonorrhea and Gonorrheal Arthritis. No article devoted exclusively to the treatment of gonorrheal arthritis with sulfapyridine appeared. Sulfapyridine was considered by Bauer and Short to be inferior to sulfanilamide for gonorrheal arthritis.

With the administration, on the average, of doses of 3 gm. a day during the first week and 1.5 gm. per day the second week, and with dependence on smears as the criterion of cure, cures were recorded in 74 to 90 per cent of cases of gonorrhea and its complications.[12, 77, 272, 377, 414, 456, 542, 567, 601, 607] Rawlins, employing cultures as the criterion of cure, with follow-up periods of six months, reported cures of cases in 96 per cent. Ferguson, Buckholtz and Hingson, employing the same rigid criteria of cure, treated 100 patients not cured by sulfanilamide; 75 per cent of them were cured by sulfapyridine in an average of seven days. They concluded: (1) inadequate treatment with sulfanilamide raises the resistance of the patient's infection toward sulfapyridine; (2) sulfapyridine is superior to sulfanilamide.

Sulfathiazole in Treatment of Gonorrhea. There were no reports on the treatment of gonorrheal arthritis with sulfathiazole.

Sulfathiazole in adequate doses (4 gm. or more per day) was used in the treatment of gonorrhea.[27, 141, 364, 380] Some physicians compared it favorably with sulfanilamide[141]; others believed it better than sulfanilamide.[27, 364, 380] Sulfathiazole is preferable to sulfamethylthiazole[364, 380] for the latter may cause serious peripheral neuritis.

Other Sulfonamide Compounds in Treatment of Gonorrhea and Gonorrheal Arthritis. By several workers sulfanilyl-sulfanilamide (disulon) was considered superior to sulfanilamide.[13, 46, 291, 582] [None of these workers required negative cultures as a criterion of cure.—Ed.] Six patients who had sulfanilamide-resistant gonorrhea, including three who had arthritis, responded promptly and favorably to disulon.[46, 291] Neuritis was noted as a complication.[46, 479, 582] Sulfanilyl-sulfanilamide was considered more effective than dimethyl-sulfanilamide.[582] Despite these claims, the percentage of cures (70 to 95) was about the same as has been reported for sulfanilamide.

Fever Therapy. Of Culp's 19 patients with gonorrheal arthritis (nine with acute, six with subacute and four with chronic), four became "well," six were "markedly improved" by fever therapy which was considered "efficacious but heroic" because of reactions. These reactions consisted of heat stroke in three cases, convulsion in one, delirium in one, and death in one case. Of Ferderber's 96 patients 70 per cent "improved." Of Trautman's 117 patients 87 per cent were "markedly improved or recovered."

Fever Therapy Plus Sulfanilamide for Gonorrhea and Its Complications. For gonorrhea, or gonorrheal arthritis resistant to sulfanilamide, Mann gave sulfanilamide 100 grains daily for two days, then six hours of fever (106.5° F. rectal): results in gonorrhea were good but "gonorrheal arthritis proved less responsive." [No details given.—Ed.] Fever therapy plus sulfanilamide cured 86 per cent of the patients of Belt and Folkenberg who had sulfanilamide-resistant gonorrhea. [No details re arthritis.—Ed.] Patients received sulfanilamide, 80 grains daily for two days prior to the first fever treatment, then 20 grains one hour before each of three fever sessions (five hours at 106.7° F.) given every other day.

Other Remedies. Culp reviewed results in the treatment of 200 cases of gonorrheal arthritis with numerous types of therapy. Sulfanilamide, mercurochrome given intravenously and fever therapy gave best results. Sulfanilamide and mercurochrome given intravenously seemed to be of equal value. Fever therapy caused more severe reactions, involved greater risks and was "more heroic" than the other two methods.

[It is interesting to note that results from mercurochrome given intravenously compared so favorably with those from sulfanilamide.—Ed.]

Autohemotherapy combined with short fever sessions was recommended for gonorrheal arthritis by Ishmael. Gonococcic vaccine was recommended by some.[122, 542]

[It is hoped that this useless form of therapy (vaccines) will soon die a natural death.—Ed.]

Tuberculous Arthritis

Clinical Data. Since bovine tuberculosis now affects only 0.4 per cent of cattle, tuberculosis in man now is due almost entirely to the human type of bacilli.[16] Clinical features of tuberculosis of spine, hip, and knee were reviewed.[204]

Diagnosis. The importance of early, correct diagnosis of tuberculous arthritis was reëmphasized by Fripp. At first the disease may be extra-articular and articular symptoms may be absent. The importance of repeated roentgenograms and synovial biopsies in doubtful cases and the advantages of microscopic examination of tissue and guinea-pig inoculations from regional lymph nodes were discussed. Negative results were inconclusive. A positive Mantoux test per se has little value, but it may corroborate other findings. There is no infallible diagnostic method in early tuberculous arthritis.

Special Localizations. Weight bearing joints are involved in about 95 per cent and those of the spinal column in 52 per cent of all cases of tuberculous arthritis.[114]

1. Spinal Column. An excellent symposium on tuberculous spondylitis was reported in 11 papers cited briefly herein; the pathology, pathogenesis and medical and surgical treatment (with end results) were discussed. [As these cannot be reviewed adequately herein original references should be consulted.—Ed.] Pott's disease accounted for 698 deaths in the United States in 1937, that is, 1 per cent of all deaths from tuberculosis.[16] Pott's disease must be regarded as a local manifestation of a general chronic tuberculous infection: its pathology was reviewed by Key.[321] Objectives of treatment should include relief of pain, healing of the spine; prevention or cure of deformity (compatible with healing), of complications and of relapses and prolongation of life.[214] Surgical fusion of the vertebrae is only an aid, and not in itself a cure for Pott's disease; prolonged general care is always advisable and surgical fusion should be postponed until forces of resistance become organized and until the lesion becomes stationary or starts to heal.[16, 105, 390, 406] Clinical features and results of surgical fusion in 1419 cases, tabulated from the symposium reports, appear in table 1.

Factors influencing end results included early treatment, severity of infection and the patient's resistance. Cleveland reported a mortality rate of 9.5 per cent among patients without active tuberculosis elsewhere than in the spinal column, and 54.5 per cent among those with active tuberculosis elsewhere. This indicates the desirability of controlling tuberculosis of lungs and other organs before attempting fusion operations.

TABLE I

Summary of Clinical Data and Results of Surgical Spine Fusion for Pott's Disease

	Authors					
	Swift	Cleveland	Meyerding	Chandler and Page	Adams	Harris and Coulthard
Cases	584	173	480	39	63	80
Follow-up, years	10+	5+	5+	5–10	5+	5+
Vertebrae affected		Chiefly lower thoracic and lumbar	Chiefly thoracic and lumbar	Low thoracic and lumbar chiefly	Low thoracic and lumbar	
Complications on admission, per cent of cases:						
Abscess		68	52	69	64	90
Paraplegia		24	17.5	8	13	16
Active pulmonary tuberculosis				13	8	30
Tuberculosis of other organs					25	30
Per cent in various age groups at operation:						
0–10	57	21	4	82	0–12	11
					100	
10–20	43	16	6	18		14
20–30		26	45			45
30–40		16	28			20
Over 40		21	17			11
Type of operation	Hibbs	Hibbs	Albee, Hibbs Osteoperiosteal graft	Hibbs	Hibbs, Albee Laminectomy Osteoperiosteal graft	Bone grafts
Results, per cent of cases "good" or "excellent"		54.2	64	74.4	60	58
Early	50					
Delayed	14					
0–10 years	72					
10+ years	53					
"Improved" or "uncertain"		19.2	11			18
"Poor" or "failure"	8	7.4	6	10.2		12
Relapse		4	3.8			10
Death	28	26.6	18	15.4	40	12
Cause of death, per cent of cases:						
Uncomplicated		9.5				
Postoperative shock or infection	5					8
Tuberculosis:						
Pulmonary	13			17		4
Meningitis	18	54.5		50		4
Other organs	22					54
Miscellaneous	42			33		30

Swett and his colleagues found no statistical advantage in operative, compared to nonoperative, treatment as determined by incidence of healing. Mayer compared results obtained by 37 patients treated surgically and 29 comparable patients treated nonoperatively: if done during active tuberculosis, fusion does not alter the course of the tuberculous process; if done during the reparative stage, it strengthens a weak spinal column and thus is beneficial. Most statistics show lower mortality rates among patients who have been operated on compared to those not operated on. [Many patients are not treated surgically because of an extensive infection or serious complication making for a poor "surgical risk." Unless comparable cases are studied, comparative results mean little.—Ed.] Surgical treatment was generally believed to be helpful, although good statistical proof is scarce.[105, 244] Chief arguments for surgical treatment are reduction in time for healing,[114] more certain healing[244] and fewer relapses. According to most investigators, fusion operations give better results in children.[114, 562] But Meyerding prefers con-

servative treatment for children and thinks results from fusion operations are better for adults.

Healing rarely occurs in the presence of an abscess, according to Swett and his associates. Hence they and others [114, 244] advised early aseptic evacuation of all abscesses. But Meyerding recommended that abscesses be left alone unless they are causing symptoms of pressure or absorption of bone.

2. Hips. Tuberculous trochanteritis must be differentiated from tuberculosis of the hip proper [586]; radical excision, resection or thorough curettage gives superior results. Although the condition is serious and disabling, the prognosis is good.

3. Knees. Arthrodesis of knees for tuberculosis can be performed successfully on children as young as 2.7 years.[231] Usually, two operations are needed; more time is required for ankylosis in younger children. In most cases there was no loss of growth; in others it was not more than ½ inch.

4. Other Sites. Wassersug described femoral trochanteric tuberculosis; in two cases peritrochanteric bursae alone were involved. A case of isolated tuberculosis of a vertebral spinous process was reported.[18]

Osteitis Tuberculosa Multiplex Cystica

No reports on this disease appeared.

"Tuberculous Rheumatism"

This questionable disease entity was not discussed.

Pneumococcal Arthritis

Pneumococcal arthritis complicates only about 0.1 per cent of cases of pneumonia and has almost disappeared since the introduction of chemotherapy.[31] Successful treatment with sulfapyridine in one case was reported.[293]

[No cultures were made from the joint; there is doubt about the diagnosis.—Ed.]

Syphilitic Arthritis and Synovitis, Charcot (Tabetic) Joints

Syphilitic Arthritis. The relationship of syphilis to chronic arthritis was studied by Kuhns and Feldman. Of 1,154 patients with chronic arthritis only 13 were found to have serologic reactions positive for syphilis. On none of the 13 could a diagnosis of syphilitic arthritis be made. They concluded that syphilis has no relationship to chronic arthritis other than as an occasional coincidental disease. Transient joint pains occur often in early syphilis. Effusions (synovitis) also may occur during the course of acquired or congenital syphilis.[128, 344]

Charcot Joints. This neuro-arthropathy affects from 6 to 10 per cent of tabetics. It may occur also in syringomyelia, injuries to cord, and leprosy. Soto-Hall and Haldeman analyzed 40 cases of tabes in which 65 joints were affected.

Average age of onset of articular symptoms was 45 to 50 years, extreme ages being 29 and 68 years. Fifty of the 65 involved joints were in lower extremities; only seven joints in upper extremities were affected. The spinal column was affected in seven cases, the sacro-iliac joints once. Trauma may explain this difference of incidence in joints of lower extremity and the rest of body. Onset of articular disease began after acute injury in almost 50 per cent of these cases. In 40 per cent involvement was bilateral. Neurologic data (Argyll Robertson pupils, absent knee jerks) were more often positive and helpful in diagnosis than were laboratory data.

Ten other cases of Charcot joints were reported.[128, 130, 158, 353] One was a case of congenital syphilis with syringomyelic dissociation and arthropathy of the elbow joint.[158] The early and progressive roentgenographic changes seen in the different joints were described.[410]

Treatment is unsatisfactory. Antisyphilitic treatment should be given but does not often affect joints; the process therein may develop and progress to destruction, even while the syphilis is being vigorously treated. Supports and braces are useful to reduce trauma to joints. The knee is most suitable for surgical procedures (arthrodesis).[391]

Brucellosis: Undulant (Malta) Fever

General reviews and discussions of public health aspects of this disease appeared.[58, 173, 264, 287, 405, 459, 460, 608]

Symptoms Referable to Muscles and Joints. Arthralgia, severe backache, neuralgia, "neuritis," myalgia, leg pains and generalized body aches are common during the acute and postfebrile periods[275, 282, 351] but cases of significant arthritis are rare. Although arthralgia and myalgia are prominent symptoms, in about half of the cases of acute brucellosis, hydrarthrosis and transient periarticular swelling occur only occasionally, and permanent articular impairment is rare.[511, 512] Cases of muscular and joint pains "resembling rheumatic fever" were again noted.[264] Among 70 cases of Greene, "rheumatism or arthritis" was the entrance complaint only once; "symptoms of arthritis" [not defined.—Ed.] were noted in only seven. Orthopedic complications include pyogenic involvement of a single joint, serous polyarthritis, and osteomyelitis generally of lumbar vertebrae according to Steindler who noted a case of acute nonsuppurative arthritis. [Data on this case were very meager.—Ed.] According to Harris "an important, and perhaps large percentage of cases of run-of-the-mill arthritis are caused by Brucella infection."

[With this we cannot agree. Harris gave no statistical proof. One of us, R. H. F., studied 25 cases of typical rheumatoid arthritis for evidence of brucellosis without success. Of 25 cases of rheumatism not typical of any common arthritis, in three active brucellosis was present and in six "possible brucellosis." It was concluded that rheumatic symptoms are common in brucellosis and temporary inflammation of joints may occur, but seldom if ever does brucellosis cause chronic, nonpurulent inflammation of joints.—Ed.]

Diagnosis. Except for isolating Brucella organisms, there is no method by which the diagnosis can be proved. Skin and agglutination tests and opsonocytophagic studies should be done in suspected cases; results should be evaluated only with clinical findings.[55, 195, 226, 264, 287, 511, 512] Chief sources of error and the inadequacies of

laboratory tests were emphasized again.[511] In many cases previous infection and active infection cannot be distinguished by laboratory tests.[39, 53, 64, 287] Skin reactions to Brucella nucleoprotein (brucellergen) and to heat-killed organisms occurred in essentially the same number of sensitized individuals.[313] Foshay preferred brucellergen for intradermal tests. Dustin and Weyler considered a febrile response (100° F. or more) to the intramuscular injection of 0.5 c.c. of a solution of 2,500,000 bacteria [presumably *Brucella abortus*.—Ed.] of significance comparable to skin reactions. [Critical comparison with results of other laboratory tests was not made.—Ed.] A modification of Huddleson's opsonocytophagic reaction was described.

Treatment of Brucellosis

Chemotherapy. Except for the sulfonamide compounds, chemotherapy has been largely abandoned.[20, 226, 511] Additional reports of cases "successfully treated" by sulfanilamide appeared[55, 108, 243, 283, 351, 418, 566] but failures were also recorded.[20, 283, 512, 536] Many believe sulfanilamide valuable chiefly in the acute stages.[20, 351] But Holland abandoned it and neoprontosil as valueless in acute cases of *Brucella melitensis* infection; his results with sulfapyridine were "spectacular." Generally, large doses of sulfanilamide (4 to 6 gm. daily) were advised[566]; a few[108, 283, 418] considered smaller doses (1.5 gm. daily) preferable. Relapses following treatment with sulfonamide compounds were frequent.[20, 275] The combined use of sulfonamide compounds and vaccine[283] or fever therapy[361] was considered better than chemotherapy alone.

In mice aldanil (sodium formaldehyde sulfoxylate derivative of sulfanilamide) and sulfanilamide gave the best therapeutic results in *Brucella abortus* infections; sulfapyridine was superior in *Brucella melitensis* infections, and sulfanilamide in *Brucella suis* infections.[332] Sulfamethylthiazole was more effective than sulfanilamide in treatment of Brucella infection in mice.[417] Toxic effects of sulfanilamide and sulfapyridine were noted.[603]

[Earlier enthusiasm for the sulfonamides in the treatment of brucellosis has waned. A definite evaluation of sulfonamide drugs on the basis of current reports is impossible. Perhaps more effective sulfonamides may be developed.—Ed.]

Serums and Vaccines. Good results were claimed for Foshay's serum.[20, 264] [It is still not available commercially.—Ed.] A method for the preparation and purification of antiserum was described.[288] "Immune transfusions" and convalescent serum were considered valuable.[275, 536] Specific vaccine therapy gave "best results" for some,[264] and was considered "preferable,"[20] "unreliable"[282] and valueless[226, 351] by others.

[The method of action is still unexplained on a sound immunologic basis.—Ed.]

Fever Therapy. Febrile responses are desired, and were thought to be responsible for benefit from vaccine treatment.[20, 511] Simpson[511, 512] reserved fever therapy for refractory cases.

Other Treatment. Ultrashort wave (6 meter) diathermy to "inaccessible foci" of (Brucella) infection such as gall-bladder and fallopian tubes was recommended by Harris [no details given.—Ed.].

[Obviously no "specific" or totally reliable treatment for brucellosis exists. More study of therapy is needed.—Ed.]

Typhoidal Arthritis

No data were reported.

Meningococcal Arthritis

In the British Expeditionary Force (1940) a mild epidemic of cerebrospinal fever occurred. Stott and Copeman noted 17 cases of chronic meningococcal septicemia without meningitis. Presenting symptoms frequently masqueraded as rheumatic fever or erythema nodosum. Present were fever, chills, headache, severe migratory joint and muscle pains. Joint effusions were not uncommon. Within a few days the characteristic rash occurred. Meningococci were found in cultures of the blood. Sulfapyridine promptly cured the disease. No suppurative meningococcal arthritis occurred.

Suppurative Arthritis

General Comment. Suppurative arthritis must be considered in the differential diagnosis of acute rheumatic fever and other acute articular disturbances.[354] Study of the frequency of recurrence of infection after elective operations in cases of healed suppuration in joints was made by Davis.[150]

Of Streptococcal Origin. A case of suppurative arthritis due to infection with Group B hemolytic streptococci (Lancefield) was reported by Rantz. This is the first case recorded in which Group B hemolytic streptococci have been recovered from suppurative arthritis of man. Group B organisms are more commonly associated with bovine mastitis and are only rarely pathogenic for humans.

Of Staphylococcal Origin. Staphylococcal septicemia and septic arthritis of the knee were successfully treated in one case by the oral use of sulfapyridine, multiple aspirations and irrigations (Kendrick[316]).

Treatment. General principles were outlined.[33, 316, 319, 354] A careful review of the recent changes in methods of treating suppurative arthritis and osteomyelitis was made by Beekman and Sullivan.

New methods of treatment are based on the fact that the bone or joint condition represents only a manifestation of a systemic condition involving a blood stream infection; hence surgical intervention should be secondary to therapy directed toward the general condition. No operative procedures should be done until the focus is reasonably well established as a bone abscess. Even then, the operation must involve a minimum of interference, yet secure drainage and relief of tension, preferably through packing of the wound in the soft parts with vaseline gauze (petrolatum) and instituting complete rest of the part by plaster encasement and infrequent dressing. Many fatalities result from too early operation; all fatalities are due to septicemia or pyemia and never to the bone lesion. In treating the general condition, whether the infection is due to hemolytic streptococci or to staphylococci must be determined, for these two organisms give rise to two distinct disease processes requiring entirely different therapy.

The new method of procedure recommended is as follows: On admission to hospital a tentative diagnosis is made and the patient's general physical condition is built up through the administration of intravenous clyses and blood transfusions when indicated. Cultures of blood and synovial exudates are made to determine the bacterial invader. The involved limb is completely immobilized in splints or by a plaster casement. A distended joint is always emptied of its effusion by aspiration before the

limb is immobilized. When the fluid equilibrium of the body is established (within 6 to 18 hours) the question of draining the lesion may be considered. In the presence of a well formed abscess in soft parts or a pyarthrosis with thick pus, operation is not delayed further. But if a thin exudate has been obtained through aspiration, or the invading organisms are hemolytic streptococci, operation is postponed. In some cases an active focus can be cured simply through immobilization of the part; in others the inflammation becomes localized by rest, and the establishment of drainage at a later date is easier and more efficient. Sulfanilamide should be given in those cases in which hemolytic streptococci are shown to be the causative agent.

The local use of sulfanilamide in cases of suppurative arthritis (and war wounds involving joints) was advised by Key, Frankel and Burford. Joint tissues tolerate the drug well but sulfanilamide should be sterilized (by autoclaving the dried powder) before being placed in clean wounds. Sulfanilamide powder slightly inhibits primary healing of wounds but not to such a degree as to contraindicate its use in clean operative wounds when infection is feared. It can be used repeatedly in open infected wounds and does not interfere seriously with the healing of such wounds.

[These conclusions were based not only on clinical experience but on animal experimentation: the treatment of experimental fractures and of experimental wounds in joints and muscles.—Ed.]

Following arthroplasty in two cases of ankylosis of knees from acute pyogenic arthritis Campbell[92] interposed a vitallium plate: the amount of motion obtained was disappointingly small.

Rarer Forms of Specific Arthritis

No new data were reported on the arthritis of scarlet fever, of ulcerative colitis, of bacillary dysentery or of lymphogranuloma venereum.

Haverhill Fever (Rat-Bite Fever). An attempt to harmonize different points of view as to the etiology of rat-bite fever was made by Allbritten, Sheely and Jeffers who tried to distinguish between rat-bite fever due to infection with *Spirillum minus* (Sodoku or Japanese rat-bite fever) and the type caused by *Streptobacillus moniliformis* (Haverhill fever). They stated that arthritis occurs only rarely in the spirillum variety.

[Two of us, W. B. and M. H. D., are unable to subscribe to the clinical distinction set forth in this article. They are of the opinion[7] that the evidence incriminating *Spirillum minus* as an etiologic agent in rat-bite fever rests on insecure grounds.—Ed.]

The relationship between pleuropneumonia-like organisms and *Streptobacillus moniliformis* was considered.[160, 329] An unusual case of arthritis caused by a "spirochete" was reported.[594] The spirochete was considered unique, unlike any previously described. Later the same type of spirochete was recovered from the blood of another patient with acute nonsuppurative arthritis of a hip: the patient had been bitten by a rat a month previously.

[Although there was no history of a rat bite in the first case, from the microphotographs and description this case might well have been due to *Streptobacillus moniliformis*.—Ed.]

Arthritis with Coccidiosis. Coccidioidal infection has long been an important public health problem in the San Joaquin Valley. It is the cause of "San Joaquin Valley fever," "desert fever" or "desert rheumatism." Symptoms of the acute form are an influenza-like onset, malaise, headache, general aches and pains in thorax or elsewhere, fever, generally bronchitis, and the appearance two to 18 days after the onset of the disease, of erythema nodosum or erythema multiforme. Smith made an exhaustive epidemiologic study in 432 cases of acute coccidioidomycosis with erythema nodosum: all patients recovered without sequelae.

Points stressed were: the difficulty of diagnosis; incubation period of one to three weeks after exposure to the spores; sensitivity to coccidioidin, a product of the causative fungus, *Coccidioides immitis,* to which sensitivity develops in from two to 17 days after the onset of symptoms, generally in the second week of illness; appearance of erythema nodosum concomitant with the development of freshly acquired allergy; contraction of the disease by inhalation of chlamydospores rather than by contact; the relationship of the incidence of the disease to climate and agricultural activities, the peak of the disease being in dusty fall and its ebb, in wet winter, and the high incidence among newcomers to the valley. Smith noted that since erythema nodosum develops in not more than 5 per cent of the cases of infection with Coccidioides, the series reported represents between 8,000 and 10,000 attacks of coccidioidomycosis.

[Smith stated that the skin lesions are often associated with "arthritis" (not defined). None of his patients had coccidioidal granuloma. This rarely develops after "San Joaquin fever," according to Smith. White females seemed to be especially sensitive to San Joaquin fever, whereas coccidioidal granuloma is prevalent among dark skinned males. Although Smith considered coccidioidal granuloma a rare sequela of San Joaquin fever, a San Joaquin Valley worker who had previously had "Valley fever" recently came to one of us, P. S. H., with chronic destructive arthritis of both ankles which was proved by biopsy to be due to coccidioidal granuloma. Coccidioidomycosis has now assumed added importance because of the location of an air training center in the San Joaquin Valley. It is being studied intensively by the public health authorities.—Ed.]

Rheumatic Sequelae of Rubella (Measles). During an epidemic of measles in the British Expeditionary Force in France, Bennett and Copeman noted the occurrence of "rheumatic symptoms," which varied from transient joint and muscle pains (15 per cent) or articular effusions, to a condition "indistinguishable from rheumatic fever."

[Is it possible that the latter cases were secondary to hemolytic streptococcal throat infections rather than to measles?—Ed.]

Rheumatic Fever

Several reviews concerned the clinical features of rheumatic carditis,[395] epidemiology,[247, 232, 255, 441, 470] theories of etiology,[299, 560] pathology,[157] therapy,[396] and public health aspects[561] of rheumatic fever.

A translation of the 1736 edition of *De Rheumatismo* by Balonius, 1538–1616,[483] and a note on the history of the disease in Great Britain[476] will appeal to those interested in medical history.

Incidence. Many good articles on the incidence of rheumatic fever appeared during 1940, including those by Hedley who estimated that rheumatic fever in its

various forms, including chorea and inactive rheumatic carditis with and without superimposed bacterial endocarditis, was responsible for 0.70 per cent of all admissions to Philadelphia hospitals, 1.56 per cent of all admissions to children's hospitals, 2.4 per cent of medical admissions to general hospitals, and 5.8 per cent of medical admissions to children's hospitals. It accounted for 50,000 patient-days annually in Philadelphia hospitals and cost these institutions more than $272,000 a year, exclusive of physicians' services. Rheumatic heart disease, including cases of superimposed bacterial endocarditis, caused 0.10 per cent of all hospital deaths in that city. [Hedley's 1940 papers have been summarized in a monograph.[252]—Ed.] In New Haven, Farquhar and Paul found that active rheumatic manifestations were responsible for 1.2 per cent of medical admissions to general hospitals and inactive rheumatic heart disease another 1.5 per cent. In Adelaide, Australia,[470] acute rheumatism accounted for 1.8 per cent of all admissions to a children's hospital and for from 0.26 to 0.33 per cent to hospitals for adults. Swift [559, 561] estimated that in New York State in 1938 more than 5,400 deaths were due to rheumatic heart disease. Contrary to common opinion, rheumatic heart disease is an important cause of death in the age groups 40 to 60 years as well as of younger persons. Swift estimated that there were about 460,000 patients in the United States who had rheumatic cardiac disease; this is a "conservative figure." The importance of rheumatic fever and rheumatic heart disease as causes of death is indicated by his calculation that they caused 14.7 deaths per 100,000 in New York City in 1938, compared with the following rates for other diseases: whooping cough 1.4; epidemic meningitis 0.7; measles 0.56; poliomyelitis 0.05. According to Clarke,[112] 0.54 per cent of the national school population of Eire has rheumatic heart disease, and 1.2 per cent of the school children in Dublin City "are probably rheumatic." Of Clawson's cases of noncongenital heart disease in which necropsy was performed, 18.7 per cent were of rheumatic origin.

Predisposing Factors Governing Incidence. 1. Geography and Climate. The relative infrequency of rheumatic fever and the rarity of typical polyarthritis in southern as compared with northern states were mentioned again; no new data were given.[24, 271, 561] The contention that the disease does not exist in the tropics was refuted again in reports from southern India.[348, 500, 599]

The rôle of meteorologic factors received more attention than in recent years. In Iowa rheumatic fever was uncommon during several dry, mild winters, but returned to its usual frequency the following wet, cold winter.[462] Hedley [250] believed the prolongation of winter's cold might be related to the increased incidence of rheumatic fever in the spring, but, considering the possible rôle of lack of sunshine, he found no indication that the amount of precipitation affected the rate of rheumatic admissions to Philadelphia hospitals. No certain relationship was found between the wetness of the season and the rate of admission to hospitals of patients with rheumatic fever in southern Australia.[470] The presence of creeks and rivers also played no etiologic rôle,[251, 470] but sections where dry heat prevailed had less of the disease than those with combined dampness, high rainfall and relatively cold temperature.[470] When this latter combination of conditions prevailed the disease was most prevalent in Eire also.[112] In an important study of environmental factors in New Haven, Paul [442] found the highest incidence in the two wettest districts investigated.

2. Season. The usual seasonal incidence in the United States, highest in late winter and spring and lowest in fall and late summer, was confirmed.[250, 554, 561]

In southern Australia [470] the incidence was high from late autumn to early spring (peak in midwinter) and lowest in late spring and early summer; winter there corresponds with the summer months in the United States. There was much less seasonal fluctuation for chorea than for polyarthritis and carditis.[112, 250]

3. Social and Hygienic Factors. The well known tendency for rheumatic fever to occur predominantly among the poor was again noted.[112, 250, 561]

Paul found no consistent increase in incidence in the poorest districts studied, but did find a fairly low prevalence in the single wealthiest district. In Australia,[470] density of population exerted a greater influence than poverty per se on the incidence of rheumatic fever; but the disease was relatively more severe in rural areas.

4. Family, Heredity, and Constitution. The increasing importance attributed to heredity in rheumatic fever in recent years was reflected in the literature.

The familial incidence was 24 per cent in one group of rheumatic patients,[462] 30 per cent in another [470] and 8 per cent among nonrheumatic controls. Perry [450] studied two pairs of apparently identical twins; both of one pair but only one of the other pair developed rheumatic fever. Perry concluded that although heredity is of considerable importance, another factor, probably infection, plays an equally, if not more, important rôle. Gauld and Read [205, 467] studied the incidence of the disease in families prior and subsequent to exposure of any member of the household to rheumatic fever. Their data supported the hypothesis that in the etiology of rheumatic fever both hereditary and environmental factors are involved and that the latter must act over a long period.

Dark eyes and hair were found more commonly in rheumatic children than in a control group.[277, 470] The distribution of the four main blood groups in rheumatic subjects was the same as in the general population.[389]

5. Sex. The hospital admission rate for rheumatic fever was essentially the same for males and females, in Philadelphia [248] and in Adelaide, Australia.[470] In the latter city chorea was slightly more common among females; in Philadelphia it was twice as common among females as among males. In Dublin 60.6 per cent of rheumatic subjects studied were females, 39.4 per cent were males.[112] Clawson's necropsy records indicate that rheumatic heart disease is about equally common among males and females, but the latter die earlier because they have more serious cardiac lesions.

6. Age. In Dublin [112] the average age at onset was reported to be 7.5 years for polyarthritis, 9.7 years for chorea; the peak incidence was about 9 years of age for polyarthritis and 10 for chorea. Both Sangster [470] and Hedley [248] found that the greatest number of first attacks occurred between the ages of 5 and 14 years. According to Gauld and Read periods of increased incidence are from 5 to 14 and from 25 to 34 years. Hedley [248] found that rheumatic fever in more than 75 per cent of cases, chorea in more than 98 per cent, rheumatic heart disease in nearly 70 per cent, begin before the age of 20 years and more than 30 per cent of deaths from rheumatic heart disease occur before this age.

7. Race. The incidence of rheumatic fever among American negroes is low [247, 554]; their unfavorable economic circumstances makes this the more striking. Natives of Uganda [599] and of Australia [470] were thought to have no racial immunity to the disease.

8. Trauma. In from 4 to 96 hours after trauma to certain joints of 12 patients, acute rheumatic episodes appeared therein.[470] The greater work of the left side of the heart is usually thought to be the reason for the predominance of rheumatic lesions

on that side; Coburn suggested that the difference in the oxygen tension on the two sides may be the cause.

General Symptomatology. Certain clinical statistics were recorded.

Acute rheumatism (including carditis) was the cause of admission to hospitals of 64.5 per cent of 450 rheumatic children, chorea, of 29.3 per cent, the two combined of 6.2 per cent.[470] On services for adults comparable figures were 83.8 per cent, 14.9 per cent, and 1.3 per cent. The distribution of manifestations in Clarke's 545 cases in Eire was as follows: rheumatic fever 42.7 per cent, insidious carditis 13.5 per cent, polyarthritis 13.5 per cent, postscarlatinal arthritis, 1.5 per cent, postscarlatinal carditis 0.5 per cent, chorea 28.0 per cent and rheumatic erythema nodosum 0.2 per cent. Rheumatic carditis occurred without a history of previous rheumatic manifestations in from 42 to 58 per cent of cases studied.[357, 462, 480]

Pathology of Rheumatic Fever: General Considerations and Special Clinicopathologic Data

An excellent account of morphologic changes in various organs was given by de la Chapelle. Cardiac lesions in rabbits which easily could have been mistaken for Aschoff bodies were noted by Loewe and Lenke. Coburn agreed with Klinge that "the apparent damage to collagen fibrils" in rheumatic lesions "really consists in an alteration of the mucoprotein ground substance."

Cardiovascular System. In keeping with their great importance, cardiac lesions received much attention, but little new information was reported.

In two series of necropsies [113, 357] the relative frequency of involvement of the various valves was given. The so-called Mönckeberg sclerosis of the aortic valve was considered rheumatic in origin.[113, 306] Contrary to the generally accepted view, another group of workers [328] considered proliferative lesions of the heart, as exemplified by the Aschoff body, to indicate that rheumatic activity has subsided. [One of us, C. M., believes that this interpretation is untenable on clinical grounds and is unsound pathologically.—Ed.] A simple "two step, cardiac function test" was used to determine when rheumatic carditis has reached an inactive stage.[346] Roth [480] found auricular fibrillation rare in young adults except as a terminal event but present in 20 to 25 per cent of those past 40 years of age. Papers appeared on the clinical features, course, and physiologic abnormalities of rheumatic tricuspid disease [15] and of pure mitral stenosis,[585] also on the clinical, pathologic and roentgenologic features of valvular calcifications in rheumatic and nonrheumatic heart disease.[177, 178]

Joints. Roth [480] believes that carditis does not occur without arthritis in children much oftener than in adults. Brief notes on the character of synovial fluid in six cases were given.[470] Features of rheumatic polyarthritis were discussed.[290, 348, 470, 473, 480, 543, 555, 599, 611] No new information was given.

Nodules. An excellent study of subcutaneous nodules of rheumatic fever and rheumatoid arthritis was reported by Bennett, Zeller and Bauer according to whom nodules in the two diseases, although similar, are sufficiently different to suggest that the two diseases may be caused by different agents. Subcutaneous nodules were present in 4.4 per cent of 450 children and in 0.6 per cent of 390 adults with rheumatic fever in southern Australia.[470] They

occurred in 5.8 per cent of children with polyarthritis and in 0.7 per cent of those with chorea.

Lungs and Pleura. The question of the frequency and, indeed, of the existence of "rheumatic pneumonia" remains unsolved.

De la Chapelle described pleural lesions but had not encountered a satisfactory example of rheumatic pneumonia. The absence of Ewart's sign in nonrheumatic pericarditis suggested to Gevalt and Levine that its presence in rheumatic pericarditis and pleuritis is due to a coexisting rheumatic pneumonitis. But Robbins and Durante warned of the danger of misinterpreting Ewart's sign to mean pneumonia instead of pericarditis.

Skin. In 5.3 per cent of 450 rheumatic children skin lesions were noted during the active infection: erythema marginatum, erythema multiforme, or an urticaria-like rash.[470]

Nervous System. The features of chorea were described.[218, 500]

In 61.4 per cent of 223 cases choreic movements were bilateral; in 26 per cent predominantly or exclusively right-sided and in only 12.6 per cent left-sided.[470] Bruetsch saw four more cases of dementia praecox, rheumatic heart disease and organic changes in the brain; he contended that rheumatic fever was a cause of dementia praecox in 9 per cent of the cases of dementia praecox he has examined pathologically.

Laboratory Data in Rheumatic Fever

Electrocardiogram. Electrocardiograms of 150 normal girls were studied by Reyersbach and Kuttner. In 5 per cent the auriculoventricular conduction time was abnormally prolonged, possibly because of increased vagal activity. It was concluded that prolongation of the P–R interval is not in itself a reliable index of myocardial involvement.

Sedimentation Rate of Erythrocytes. This was again considered the most important single laboratory test of rheumatic activity.[87, 385, 402, 555, 584, 587]

Hemoglobin. In the presence of a rapid sedimentation rate, Wallgren considered a decreasing level of hemoglobin evidence of persisting serious activity but a rising level of hemoglobin favorable.

Blood Chemistry. Phosphorus in the blood of rheumatic children was found to be relatively low.[179]

Weltmann Reaction. In chorea this test gave usually normal or increased values; in polyarthritis and carditis values were low but returned to normal earlier than the sedimentation rate.[328]

Relationship of Rheumatic Fever to Other Diseases

Rheumatoid Arthritis. As has been mentioned, histologic differences in the subcutaneous nodules of rheumatic fever and rheumatoid arthritis suggested to some[42] that the two diseases are of different etiology.

Subacute Bacterial Endocarditis. The importance of rheumatic heart disease in preparing the way for subsequent bacterial endocarditis was pointed out.[247, 357] Subacute bacterial endocarditis in 64.5 per cent of Hedley's[248] 324 cases was regarded as superimposed on rheumatic heart disease.

Sydenham's Chorea. Chorea generally was accepted as a manifestation of rheumatic fever.[79, 213, 218, 248, 290, 385, 468, 500] Struthers stated that rheumatic heart disease was likely to develop in cases of chorea only when polyarthritis also was present, but Hedley [247] found that rheumatic heart disease developed in 46.5 per cent of 4,616 cases of chorea and that even in 28.8 per cent of 526 cases of so-called pure chorea, rheumatic heart disease was diagnosed.

Erythema Nodosum. It is believed that certain cases of erythema nodosum are of rheumatic origin and others not.[112, 470]

Differential Diagnosis in Rheumatic Fever

Discussed were the differentiation of rheumatic and nonrheumatic "growing pains" [24, 290, 385] and rheumatic and syphilitic heart disease.[90, 494] Clawson found pericarditis so frequently at necropsy in cases of subacute bacterial endocarditis that he argued that the presence of pericarditis cannot be used clinically in differentiating between that disease and rheumatic carditis. [We cannot agree with this clinical conclusion.—Ed.] The danger of mistaking pericarditis with effusion for lobar pneumonia was emphasized.[472] Other diagnostic difficulties were discussed.[84, 569]

Prognosis and End Results of Rheumatic Fever

The immediate mortality in the first attack of rheumatic fever is low, especially among adults; this was again shown by an analysis of results of the first attacks on 405 children and 309 patients more than 12 years of age.[470]

The immediate mortality rate was 4.69 per cent for the children, only 0.32 per cent for the adults. For the total of 714 patients the immediate mortality rate was 2.8 per cent. Hedley [249] estimated that 3.5 to 4.5 per cent of first attacks terminated fatally. But Gibson [213] took a more gloomy view; in his 146 fatal juvenile cases, death occurred within one month of the onset in five, within four months in 19, and within one year in 20 more. To him nodules and pericarditis were of serious prognostic significance; chorea and rheumatic erythemas indicated relatively mild infection. In contrast Struthers regarded erythemas and epistaxis as of serious import. Many believe that the older the child at the initial rheumatic attack, the less likely is carditis to result, but others [554] found no indication that children whose first attack was in early childhood died sooner thereafter than those whose first attack came later. As between onset during childhood and adult life, there seems to be no doubt that the prognosis is distinctly better in the latter.[395, 470]

Death and the onset of heart failure in cases of old rheumatic heart disease usually are due to a recrudescence of rheumatic activity; this is especially true of children and young adults.[213, 249] Thus it is important to recognize the signs and symptoms of carditis and of rheumatic activity in general: these were reviewed.[273, 395, 396 543, 555] The relative seriousness of aortic and mitral valvular lesions remains debatable.[113, 480, 585]

The serious ultimate prognosis was stressed. In follow-up studies of large groups of rheumatic children mortality rates of 15 to 30 per cent were recorded over periods of 10 to 18 years.[385, 554] Among Hedley's[249] 542 fatal cases, death from the primary rheumatic manifestation resulted in less than one year in 13.5 per cent, in less than five years in 32 per cent, in less than 10 years in more than 48 per cent. Although the outlook is serious once rheumatic heart disease has developed, the heart

does not always receive significant injury. Thus, of Gibson's 1,487 patients with rheumatic fever or chorea, 42 per cent escaped evident heart disease. In a study [479] of 523 first attacks, 66 per cent of the patients at the time of dismissal were thought to be without cardiac damage, as were 50 per cent of the 175 patients of Brown and Wolff followed for an average of seven years.

Pregnancy in Rheumatic Heart Disease. Data on maternal and fetal mortality rates and on various clinical features were given.[109, 221, 249, 357, 554] The maternal mortality rate ranged from 2.2 to 18.1 per cent. Pregnancy seems to protect rheumatic subjects against recrudescences of rheumatic activity after hemolytic streptococcal infections.[115]

[This is interesting, especially in view of the ameliorating effect of pregnancy on rheumatoid arthritis.—Ed.]

Rheumatic Fever and Jaundice. Three patients with rheumatic fever had jaundice; two may have been benefited by the jaundice.[256]

Etiology and Pathogenesis of Rheumatic Fever

Factor of Infection. Infections of the upper respiratory tract preceded 34.2 to 86 per cent of rheumatic attacks.[112, 299, 470] Jones and Mote found infections of the respiratory tract preceding 58 per cent of first attacks and 67 per cent of recurrent attacks of rheumatic fever. In most of the cases without clinical evidence of respiratory infections there was serologic evidence suggesting recent infection with hemolytic streptococci. Suppurative and highly invasive infections are rarely followed by rheumatic recrudescences, according to Coburn.

1. Skin Tests. Contrary to most earlier reports, Jones [299] stated that reactions to intradermal injections of streptococcic products were no greater in rheumatic subjects than in control groups if the opportunity of streptococcal infections was similar. Green [224] noted dermal reactions in a normal subject tested with synovial fluid from three patients with rheumatic polyarthritis; the reaction could be "neutralized" by mixing serum from convalescent rheumatic patients with the fluid.

2. Antifibrinolysins. Boisvert noted that antifibrinolysin titers of rheumatic children usually remained high longer than those of most nonrheumatic children suffering from simple hemolytic streptococcal infections.

3. Antistreptolysins. According to Coburn, in cases of infections with hemolytic streptococci without subsequent rheumatic fever, the antistreptolysin titer rises no later than two weeks after the initial infection, but in cases of rheumatic fever titers rise in the third week and remain high as long as the disease remains active. Bunim and McEwen noted that titers tended to be normal in inactive rheumatic heart disease but high in the active manifestations, including chorea. There was no apparent relationship between the height of the titer and the severity of the disease.

All previous studies on antistreptolysin in rheumatic fever, including those just mentioned, dealt with so-called antistreptolysin O. Todd, Coburn, and Hill studied another variety, antistreptolysin S. This antibody increases after hemolytic streptococcal infections as does the other, but, in contrast, it tends to be lower during bouts of rheumatic fever; thus its behavior differs notably from that of the antistreptolysin O titer.

4. Complement Fixation Tests. From liver and spleen of a rheumatic patient Coburn prepared an antigen which fixed complement in the presence of fresh rheumatic fever serum.

5. Interpretation. The obvious interpretation of these data is that hemolytic streptococci bear an important etiologic relationship to rheumatic fever.[300, 470, 559, 560] According to Coburn heredity and environment combine to produce persons who do not handle respiratory infections with hemolytic streptococci in a normal manner. Their immune response to the primary infection is inadequate with the result that the cells of the reticuloendothelial system become sensitized. Subsequent contact of antigen and antibody within the sensitized cells gives rise to an abnormal reaction leading to the characteristic inflammation of rheumatic fever.

[This stimulating paper deserves the attention of all students of the disease.—Ed.]

6. Culture of Synovial Fluid. From three of six specimens of synovial fluid a gram-positive, spore-bearing bacillus was isolated.[470] No etiologic significance was attached to it.

Virus Theory. Inoculation of fluids from four joints and of suspensions made from two subcutaneous nodules into monkeys gave negative results.[470] Spinal fluid from six choreic children was inoculated intracerebrally into rabbits by Loewe and Lenke. In some of the rabbits cardiac lesions were found which closely resembled those of rheumatic fever, but they were also found in control animals, hence they had no etiologic relationship to rheumatic fever. Eagles and Bradley retracted their previous statement that so-called elementary bodies found by them in rheumatic exudates might possibly be of etiologic significance. Swift,[560] Sabin and Johnson found no pleuropneumonia organisms in rheumatic patients and concluded that these agents are not concerned in the disease. A virus was isolated from human rheumatic material by Jones [299] but it was apparently that of influenza, and was unrelated to rheumatic fever.

Factor of Vitamin Deficiency. Monkeys were rendered scorbutic and then given intratonsillar injections of hemolytic streptococci, one strain of which was of monkey origin: results were negative.[470] Although vitamin C deficiency is present in rheumatic fever, feeding adequate amounts of the vitamin will not prevent the disease.[303] There is no proof that vitamin C deficiency is more deleterious in rheumatic fever than in any other infectious process.[299]

Conclusions on Etiology. The reports of 1940 indicate that the promising work of the past few years on a possible virus etiology of rheumatic fever has led to disappointing results. The importance of infection with Group A hemolytic streptococci becomes more and more apparent, but whether these bacteria are the primary, or merely an important contributing, cause still has not been proved. Why rheumatic attacks develop after such infections in some cases and do not in others remains a vexing question. That heredity and environmental factors each are concerned grows increasingly clear. It should be noted that bacterial hypersensitivity again was suggested as playing a rôle by a new and authoritative voice (Coburn).

Treatment of Rheumatic Fever

General Remarks. The treatment of all aspects of rheumatic fever was discussed.[49, 383, 393, 396, 560, 571, 611]

Rest. The extreme importance of rest was again stressed.[273, 383, 393, 554, 571, 584, 611] Rest probably aids, in part, by diminishing tachycardia, thus

lessening the cardiac load.[560] Home occupational therapy was considered valuable.[532]

Salicylates. If ordinary doses of 60 to 150 grains daily do not relieve polyarthritis, the amount should be increased to 200 or more, according to Marquis who gave up to 390 grains daily for short periods. Salicylates are of great value in combating polyarthritis, fever and toxic manifestations of rheumatic fever, but they do not affect the fundamental course of the disease.[49, 56, 87, 396, 584, 611] A new and (if confirmed) important use of salicylates was reported by Boas and Ellenberg who obtained dramatic diminution of the effusion in 12 cases of pericarditis with effusion; myocarditis and endocarditis were unaffected.

Sulfanilamide. Additional reports[286, 537] of the ineffectiveness of sulfanilamide in the treatment of rheumatic fever were made.

[For its prophylactic use, see later.—Ed.]

Removal of Foci of Infection. Upheld was the opinion that tonsillectomy is of minor, if any, importance in the treatment and prevention of rheumatic fever; the decision to perform the operation must be made in each case on the basis of the laryngologic indications.[101, 112, 286, 357, 383, 393, 402, 537, 555] Gingivitis or infected teeth play no evident rôle.[402]

Vaccines and Serums. Treatment with vaccines and serums has had little support in recent years but several reports during 1940 advocated their use.

Cecil suggested that "streptococcus vaccines" may have prophylactic value if given yearly. Wasson and Brown reported a much lower incidence of rheumatic exacerbations among patients given a broth filtrate of hemolytic streptococci than among controls.

[This is contrary to previous results with vaccines.—Ed.]

To 15 patients with acute rheumatic fever Green and his colleagues[225] gave serum from convalescent rheumatic patients: nine were "benefited."

[This work needs confirmation; a number of unpublished trials of convalescent serum in rheumatic fever have given negative results.—Ed.]

Diet and Vitamins. Vitamin C supplements have no curative or prophylactic effect in this disease; even so it may be important to correct the low blood vitamin C levels usually present.[303, 571] Kuttner found no decrease of upper respiratory infections in a group of rheumatic children fed large doses of vitamins A, B, C, and D, as compared with a control group not receiving the vitamin supplements: three children experienced rheumatic attacks while taking the vitamins.

Treatment of Chorea. Fever therapy was recommended for severe chorea.[185, 263, 271, 530, 611] (It was valueless in 11 cases of rheumatic carditis treated by Heymann and Enright.) Hughes warned of the dangers of nirvanol. In five cases Hollander used intramuscular injections of lipoids extracted from ox brain: the chorea cleared in six to eight days.

[The author's explanation of the possible mechanism involved is not convincing but the method deserves investigation.—Ed.]

Institutional Care and Climate. It was Swift's[561] "firm conviction" that "the average child in the subacute and chronic stages of rheumatic activity would be best treated in an institution where the special indications imposed by his disease can be adequately met."

Swift[559] summarized these indications thus: "To build up the patient's resistance against infection; to provide prolonged rest and thus reduce to the lowest possible level the damage to inflamed organs such as heart and blood vessels; to regulate exercise carefully so that a diseased organ may be slowly restored to its most effective physiological capacity; to provide suitable education in a psychologically proper atmosphere." A convalescent hospital in Sydney, Australia, was described.[290] In reviewing 15 years' experience at the Children's Heart Hospital of Philadelphia, Stroud and Twaddle did not find that prolonged hospitalization materially decreased the death rate nor increased the number of patients able to lead active lives in later years.

No new data on climatotherapy were given.[299, 396, 561]

Treatment of Pregnant Rheumatic Cardiacs. Special procedures used on two large obstetrical services were outlined.[109, 221]

Prevention of Rheumatic Fever

Prophylactic Value of Sulfanilamide. The prophylactic value of sulfanilamide in rheumatic fever was reaffirmed by Coburn and Moore who brought their experience with it up to date: rheumatic exacerbations developed in only one of 184 children given prophylactic doses of sulfanilamide as compared with their occurrence in 35 per cent among their children not so treated. The drug was given in doses of 2 to 3 gm. daily throughout the school year—sufficient to maintain blood levels of 4 to 5 mg. per cent. Toxic symptoms appeared in about 10 per cent of cases. But some children, given sulfanilamide during convalescence from recent rheumatic attacks, developed recrudescences.

Public Health Aspects. Growing interest of public health departments in rheumatic fever was illustrated in the decision of the Central Board of Health of South Australia to conduct the valuable epidemiologic survey[470] frequently referred to herein. Rheumatic fever, chorea, and cardiac disease cause twice as many deaths among Australian children 10 to 15 years old as tuberculosis does. Clarke[112] described efforts made in Dublin to meet the problem. American needs were outlined by Swift.[559, 561] Based on an average rest in bed of six months for each patient and the experience in London, New York City would require about 1,750 beds for the care of rheumatic patients; actually there are only 300 to 400.

Chronic Arthritis: The Two Common Types

In previous Reviews we have used the terms "atrophic" and "hypertrophic arthritis," terms used by the American Rheumatism Association. To foster closer relationships with the rest of the English speaking world the Association recently adapted as preferred terms "rheumatoid (synonymous with chronic infectious, atrophic or proliferative) arthritis" and

"osteo-arthritis or degenerative joint disease (synonymous with hypertrophic or senescent arthritis)."

Rheumatoid (Chronic Infectious, Atrophic, Proliferative) Arthritis

Influence of Heredity on Incidence. In an Italian series the familial incidence of rheumatoid arthritis was about 30 per cent; affected were two boys and two girls in one of the families studied.[464] Concerning this factor Horder [280] wrote: "Obviously we cannot take measures to cure our ancestors. But [by eliminating other predisposing factors] we can use diligence to see that our posterity has less cause to reproach us."

Clinical Data. The various stages of the disease were described, also the minimal requirements for a diagnosis of rheumatoid arthritis [102, 258, 259] and the differentiation of early rheumatoid arthritis from periarticular fibrositis.[516] Projection of articular pain was discussed by Werndorff. As a rule pain in joints is not projected; an exception is the extension of pain from arthritic hips to sciatic region, groin or knees. Pain in the knees in coxitis is caused by pressure: granulation tissue growing in the acetabular fossa as a result of synovial involvement presses on the obturator nerve.

[This explanation is not wholly satisfactory. Pain may be referred to knees from osteo-arthritic hips in which cases significant synovial involvement does not occur.—Ed.]

Rheumatoid Arthritis: Special Clinical Features

Effect of Hepatitis and Jaundice. Usually considered an enemy to man's well being, hepatitis with jaundice may be distinctly advantageous to patients with rheumatoid arthritis who, with the onset of significant jaundice, may suddenly lose for a time all symptoms of active disease.

Between 1933 and 1939 this phenomenon was noted 72 times: in 45 cases by Hench, in 27 cases by others.[256] "Gold jaundice" from chrysotherapy may or may not provoke the phenomenon.[6] A patient given injections of sanochrysin by Cecil [102] had no notable relief until toxic hepatitis and jaundice suddenly developed presumably from gold. "Within a week or so after the onset of jaundice, swelling and pain disappeared entirely from the joints and there was complete restoration of function." This remission lasted more than three months. Recently cases have been noted in which jaundice apparently induced temporary but impressive remissions from migraine, ragweed hay fever and egg sensitivity. Discussing these probably related phenomena Hench raised certain questions. Are hepatitis and jaundice anti-allergic? Is rheumatoid arthritis caused by an unknown type of hypohepatia or hyperhepatia which becomes temporarily corrected incident to hepatitis of the proper degree and type? The phenomenon proves that rheumatoid arthritis is not inherently irreversible; obviously the body of the arthritic patient, if properly stimulated, can correct quickly and effectively the disturbed physiology underlying the disease. Further study of this phenomenon may reveal some "biochemical flaw" responsible for the disease.

[One of us, R. H. F., noted that the serum lipids of patients with rheumatoid arthritis are not below normal; hence jaundice is not beneficial to arthritic patients by reason of correcting a lipid deficiency.—Ed.]

Effect of Pregnancy. The ameliorating effect of pregnancy on rheumatoid arthritis was discussed.[166, 435] According to Dunn the relief may be correlated "most probably with the high estrogenic blood content of pregnancy." Arthritic patients may receive complete, partial or no relief during pregnancy. "The estrogen content of the blood and urine in pregnancies, while always high above normal, varies widely in individual pregnancies. Accordingly, a failure to obtain relief of the arthritis in all pregnancies does not invalidate its rôle."

[An attempt should be made to correlate the degrees of relief experienced by arthritic patients during pregnancy with amounts of estrogenic hormone found in their blood. But it seems probable that some factor other than an increase of estrogenic substances in blood is responsible for the ameliorating effect of pregnancy.—Ed.]

Ocular Lesions with Rheumatoid Arthritis. Of 15 cases of necroscleritis nodosa (scleromalacia perforans, scleritis necroticans) reported to date, 11 have been in patients with rheumatoid arthritis.[6] Some writers believe that the subcutaneous nodules of rheumatoid arthritis and the nodules of scleromalacia perforans are essentially similar in their early stages. Eggers reported the case of a woman, aged 37 years, in whom rheumatoid arthritis and necroscleritis nodosa developed almost simultaneously. Bilateral uveitis, massive hemorrhages in the vitreous, and sclerosing keratitis ensued. Biopsy showed that the ocular nodules represented intrascleral abscesses. "The simultaneous involvement of sclera, bones and joints need not seem strange if one remembers that all three tissues are of mesodermal origin."

No adequate reason has been given to explain why iritis and uveitis not infrequently complicate rheumatoid arthritis. Hence Angevine and Rothbard[7, 19] studied eyes and joints of rabbits infected with various bacteria. In 26 of 40 rabbits arthritis developed, in 17 ocular lesions. When arthritis or cyclitis occurred, synovial villi and ciliary processes were the most frequent, and usually the primary, sites of inflammation; bacteria were found therein.

Amyloidosis with Rheumatoid Arthritis. Amyloidosis may complicate rheumatoid arthritis or Still's disease.[7] Oxer studied two men aged 21 and 27 years who had rheumatoid arthritis of 11 and 13 years' duration, with iritis or iridocyclitis and blindness; marked anemia occurred in both cases, hepatomegaly in one. At death amyloidosis of liver, spleen and kidneys was noted. "Suppuration is not necessary to produce amyloidosis." Splenic amyloidosis was also found[145] in a case of "Felty's syndrome" [i.e. rheumatoid arthritis.—Ed.].

Pathologic Characteristics of Rheumatoid Arthritis

The pathologic physiology of joints in rheumatoid and other types of arthritis was discussed by Freund and Kelikian who described how articular structures react to abnormal stimuli.

Within normal joints, resting or in motion, there is a negative intra-articular pressure equal to –60 or –70 mm. of water. Under pathologic conditions, such as intra-articular effusions or hemorrhage, intra-articular pressure becomes positive, as high as + 70 mm. of water [sometimes as high as + 700 mm.—Ed.]. The capsule becomes distended. If cartilage is damaged or if bone is atrophic as in rheumatoid arthritis, the increased intra-articular pressure may push contents of the joint cavity through defects of cartilage or underlying bone. If the opening is small, a flasklike excavation results; when pressure is severe and prolonged, deep cavities result. In rheumatoid arthritis these cavities contain fibrinoid masses which begin to organize. These ex-

cavations may be numerous and appear like epiphyseal cysts or abscesses. To prevent them effusions should be removed by aspiration or other means before too long.[199]

[It seems to us more likely that such lesions result from enzymatic action or from the invading pannus.—Ed.]

Nodules. Italian rheumatologists [464] believe that the subcutaneous nodules of rheumatoid arthritis resemble histologically those of rheumatic fever but that neither are specific nor diagnostic. Bennett, Zeller and Bauer contradicted this view.

"The nodules of rheumatoid arthritis and rheumatic fever differ as much from one another as do the granulomas of syphilis and tuberculosis." The nodules of both rheumatoid arthritis and rheumatic fever have certain structural and cytologic similarities, but differentiation is generally possible because one or more of the pathologic alterations usually predominate. Nodules of rheumatic fever usually exhibit injury to small blood vessels with exudation of plasma and blood cellular constituents into connective tissue, also small focal lesions similar or identical to the myocardial Aschoff nodules. In the nodules of rheumatoid arthritis marked proliferation and degeneration of connective tissue predominate, Aschoff-like nodules are rarely seen, and exudation is rarely notable. Hence the nodule of rheumatic fever, being chiefly an exudative phenomenon, tends to appear and disappear rapidly. The continued proliferation and necrosis of the nodule of rheumatoid arthritis explain its longer duration and larger size. These morphologic changes do not permit conclusions on etiology.

Muscles. Pathologic reactions (an "angiomyositis") in muscles of the calf in four cases of rheumatoid arthritis were considered by Curtis and Pollard similar to those in eight cases of adult Still's disease. They are described in the section on "Still's disease."

Laboratory Data in Rheumatoid Arthritis

Roentgenograms. Roentgenographic features were summarized.[529] Especially informative was the report of Forestier and Robert which cannot be adequately reviewed here. In mild cases "roentgenograms may be negative for a period of several weeks to two or three months."

Blood Counts. A mild anemia of normocytic or microcytic type does not appear until the disease has been active "for several weeks" (Farrar and Rayburn). Leukocyte counts may be from 12,000 to 20,000 in acute febrile cases, 4,000 to 11,000 in chronic cases. The percentage of nonfilamented cells was more than 16 per cent (maximal normal) in 63 per cent of 234 cases, and more than 8 per cent in 88 per cent of 392 cases. "A normal nonfilament count usually excludes active rheumatoid arthritis." [183]

Among normals, according to Stiles, Dirickx and Stiles, the nonfilamented neutrophiles range from 2 to 5 per cent of the total number of leukocytes, with a mean value of 4.1 per cent. Filamented neutrophiles range from 55 to 66 per cent, with a mean value of 60.6 per cent. The nonfilament-filament ratio (nonfilamented neutrophiles times 100 divided by filamented neutrophiles) ranges from 3 to 9 (av. normal mean 7). In 14 cases of rheumatoid arthritis the mean nonfilament-filament ratio was 36.9, a significant increase.[546] This ratio was found to be a more sensitive indicator of arthritic variations than the sedimentation rate, but the latter is of more fundamental significance. When remissions occur, the nonfilament-filament ratio

may fall but the sedimentation rate may remain elevated for some time, a warning that conditions are not yet normal.

Sedimentation Rates. It is generally agreed that sedimentation rates of erythrocytes are increased in practically all cases of rheumatoid arthritis.[183, 464]

Of 568 cases noted in the literature rates were increased in 92 per cent. (Rates were normal in 60 per cent of 254 cases of osteo-arthritis, in 75 per cent of 149 cases of fibrositis.) Rates may not be increased during the first weeks in acute cases or during the early months in the more insidious cases.[183] The mean rate in Stile's 14 cases was 37.3 mm. (Westergren method, uncorrected for anemia). But rates were normal in 50 per cent of 435 ambulatory patients with rheumatoid arthritis seen by Weil, Smith, King and Wooton who considered the value of the test overrated. [The reported details of these cases were meager.—Ed.] Rates varied from 20 to 125 mm. (Westergren method) in 43 active cases, from 8 to 20 mm. in eight arrested cases reported by Davison, Woolley and Donovan who noted no constant relationship between sedimentation rates and concentrations of plasma proteins. Repeated blood transfusions were followed by reduction in sedimentation rates without improvement in plasma protein relationships.

Serum Proteins. Most of the patients of Davison, Woolley and Donovan exhibited increased fibrinogen and serum globulin, normal serum albumin (reputedly generally increased),[183] normal total proteins and reduced albumin-globulin ratios. There were many exceptions, however, as shown in table 2 [and as noted in our last Review.—Ed.]

TABLE II

Values for Serum Proteins *

(Davison, Woolley and Donovan)

	Normal Controls (7)	Rheumatoid Arthritis	
		Clinically Inactive (8 cases)	Active (43 cases)
Serum fibrinogen	0.2–0.4	0.3– 0.6	0.2– 0.8
Serum albumin	4.6–5.6	4.7– 6.0	2.4– 7.1
Serum globulin	1.9–3.0	0.4– 2.9	0.3– 5.1
Albumin-globulin ratio	1.7–2.5	1.5–14.3	0.6–15.0
Total proteins	6.6–8.3	5.7–10.0	5.0– 9.8

* All values except albumin-globulin ratio expressed in grams per 100 c.c. of serum.

Miscellaneous. The formol-gel test provides a simple qualitative test for increased globulin or fibrinogen in the blood. It depends on the change in viscosity of blood fluids after the addition of formaldehyde.[6] Normal serums and plasmas undergo little if any physical change, but specimens containing excess globulin or fibrinogen undergo a marked increase in viscosity which may induce complete coagulation or irreversible gelation of the fluid. Scull and Pemberton noted that gelation generally occurred in cases of rheumatoid arthritis and to a more marked degree than in cases of osteo-arthritis. There was a significant association between formol-gel reactions and sedimentation rates: when the former were negative, the latter were generally normal.

[We believe that sedimentation rates provide the more accurate index of clinical activity of the disease.—Ed.]

Serum phosphatase is generally normal in chronic arthritis.[7] Some workers have noted normal values in rheumatoid arthritis, increased values in osteo-arthritis.[588]

Watson considered normal values to be up to 5.0 Bodansky units per 100 c.c. of serum. Among 45 patients with "chronic arthritis" (types not separated) values ranged from 4.4 to 14 (average 9.1) units.

Etiology and Pathogenesis of Rheumatoid Arthritis

Factor of Infection. 1. Foci. Of 53 cases of rheumatoid arthritis in which foci had been removed previously Bach found the following infected foci still present: gingivitis in 44, infected teeth in 25, infected dental roots in 10, infected tonsils in 11, infected tonsil tags in nine, sinusitis in 11, cholecystitis in five, cholelithiasis in four; prostatitis in seven of 17 males, cervicitis in seven of 36 females. Of these 53 patients only two had no infected foci, 10 had one, 14 had two, 19 had three, six had four. [This adds up to only 51 patients.—Ed.] Examination for, and removal of, foci too often are hastily and incompletely done.

By using certain in vitro tests Stiles and Chapman recovered bacteria, considered pathogenic, from various foci in 16 cases of rheumatoid arthritis: *Staphylococcus aureus* from nose in 44 per cent, from oral cavity in 19 per cent; alpha streptococci from feces in 38 per cent, from nose in none. Similar organisms were as readily found in foci of patients with a variety of chronic illnesses.

Four writers [22, 444, 598] considered infected gall-bladders a significant focus in arthritis. Peers obtained abnormal cholecystograms in 13 of 25 cases of rheumatoid arthritis (in 13 of 21 cases of osteo-arthritis). Willard and Strawbridge considered studies of biliary drainage a necessary adjunct to cholecystograms. Pathogenic organisms (*Escherichia coli* or *Bacillus coli, Staphylococcus aureus,* nonhemolytic or green-producing streptococci, a member of the salmonella group) were found in biliary drainages from 35 per cent of 29 patients with "arthritis" (type not stated).

[No data were given to show whether these patients were relieved of their arthritis when gall-bladders were removed. Very few patients with cholecystitis develop rheumatoid arthritis. Other writers [1] have previously noted no permanent benefit from removing infected gall-bladders in cases of rheumatoid arthritis.—Ed.]

It must take more than an infected focus, however, to produce arthritis. In 63 per cent of 239 psychiatric patients ("physically well," that is, "mentally rather than physically ill") C. H. Brown found infected foci. Yet none of these patients had arthritis. Infected foci were found in the nose and throat in 44 per cent of these cases, in the teeth in 37 per cent, in female pelvic organs in 22 per cent, in urinary tract in 17 per cent, in cardiorespiratory system in 2 per cent; foci of infection in chests were rare.

2. Cultures of Blood and Joints. Findlay and his colleagues could not isolate pleuropneumonia-like organisms from the synovial fluid of four patients with rheumatoid arthritis or from the pleural and pericardial exudates from two other rheumatoid patients.

3. Precipitins. In 69 per cent of 32 cases Bruce and Caswell found precipitins to hemolytic streptococci in high titer in serum; similar precipitins

were found in only four of 15 cases of osteo-arthritis, in none of 10 normal controls. The presence of these precipitins was considered indirect evidence that streptococci play some, possibly an etiologic, rôle in the disease, or such precipitin reactions may be specific for rheumatoid arthritis but without etiologic significance.

4. Agglutinins. In 72 cases Bunim and McEwen studied the agglutination titer for hemolytic streptococci: in 14 it was negative; in four, 1:20 or 1:40; in the others (75 per cent) significantly elevated: 1:80 or 1:160 in 23; 1:320 or 1:640 in 31 cases.

5. Antistreptolysins. In most of the 72 cases of Bunim and McEwen antistreptolysin titers were not abnormal. In normals the median titer was 25 units, the normal maximum was 100 units. Antistreptolysin titers were 100 units or less in 61 cases; 150 to 400 units in 11 cases of rheumatoid arthritis. These generally normal values contrasted sharply with the elevated agglutinin titers. In three-fourths of the cases of high agglutinin titers antistreptolysin titers were normal. Since no correlation was noted between the antistreptolysin titer and the stage of the disease or severity of illness, such titers were of doubtful prognostic import.

6. Antifibrinolysins. Antifibrinolysin titers were normal in 161 of 171 tests made by Perry [451] in 33 cases of rheumatoid arthritis; in only two cases were abnormal titers found and these were only transient. These results are in striking contrast to those in rheumatic fever.

[In other words these data do not support the idea that hemolytic streptococci cause rheumatoid arthritis, and are evidence against the idea of a common etiology of rheumatic fever and rheumatoid arthritis.—Ed.]

Theory of Bacterial Allergy. Italian work reviewed by Ravenna yielded no support to this theory. But Cecil believes that the theory needs further study and in its support cited unpublished work of Angevine and Rothbard on the sensitization of joints of animals to experimental arthritis.

Virus Theory. No data appeared.

Factor of Trauma. This was not discussed.

Factor of Circulatory Disturbance. The abnormal sugar tolerance curves commonly found in cases of rheumatoid arthritis have been considered caused by circulatory disturbances in finer vessels rather than by disturbed pancreatic function.[464, 498] To verify this concept Dandurand, Scull and Pemberton applied to the blood of 55 rheumatic patients (23 with rheumatoid arthritis, 14 with osteo-arthritis, 11 with "mixed arthritis," three with fibrositis, four with miscellaneous rheumatic conditions) the test of Polonovski and Warembourg (1933) for fractionating the glucose and non-glucose materials in blood which reduce chromic acid. The blood plasma of these "rheumatisants" regardless of type, generally possessed an excess of reducing substances other than glucose. Wide individual variations were found, the significance of which was not clear. Tests were repeated after the ingestion of glucose. Results were interpreted as indicating that delayed

responses to the sugar tolerance test reflect circulatory alterations, not a primary disturbance in carbohydrate metabolism.

Factor of Altered Metabolism. Advocates of sulfur therapy have reported that a deficiency of sulfur exists in nails, articular cartilage and other tissues of arthritic patients, indicating an abnormal sulfur metabolism. But these reports have given meager or contradictory data. The careful, detailed studies of Freyberg, Block and Fromer in four cases of rheumatoid arthritis, two of osteo-arthritis, three of ankylosing spondylitis and on four normal controls led to opposite conclusions as follows:

No evidence of sulfur deficiency or abnormality of sulfur metabolism exists in arthritic patients. There is no obvious biochemical or metabolic indication of a need for, or benefit from, sulfur in the treatment of arthritis. The distribution of urinary sulfur was about the same among these various patients and controls except that arthritic patients eliminated a slightly higher percentage of sulfur in conjugated form. Even if the difference were significant, it does not indicate a deficiency of sulfur for purposes of detoxication or any impairment of the detoxifying function in cases of arthritis. The effect of colloidal sulfur injected intravenously was about the same on arthritics and controls. Since the excretion of sulfur increased by amounts greater than those injected, the intravenous injection of colloidal sulfur assuredly would not benefit or prevent sulfur deficiency if it existed. Since no consistent significant increase in excretion of conjugated sulfur resulted, significant detoxification cannot result from such injections. When colloidal sulfur was injected intramuscularly, more than the amounts injected appeared in urine; hence such injections tended to increase rather than prevent sulfur deficiency. No notable change in excretion of conjugated sulfur occurred. Whether given by vein, muscle or mouth, colloidal sulfur was metabolized and excreted in the same way, indicating no advantage to its parenteral use. The cystine content of finger nails was normal in most cases of arthritis, unexplainably low in a few. But the administration of large amounts of colloidal sulfur or sulfur containing salts did not increase the cystine content of nails.

[This excellent study indicates the complete irrationality of sulfur therapy for arthritis. If those who would propose a "new form" of treatment would only carry out careful studies such as this before advocating the new remedy, physicians and patients would not have to waste so much time and money on useless remedies and therapeutic fads.—Ed.]

Factor of Vitamin Deficiency. 1. Vitamin A. Patients with rheumatoid arthritis were found by Race [5] to be deficient in plasma vitamin A. Using a different method, Hall, Bayles and Soutter noted a borderline to severe vitamin A deficiency in 65 per cent of 79 cases. In 45 cases the degree of vitamin A deficiency roughly paralleled the severity of the disease as indicated by sedimentation rates.

Race [5] studied his cases by means of the light-extinction density. Direct chemical and spectrographic methods for measuring the quantity of vitamin A are inaccurate. Vitamin A unites with proteins in retina to form visual purple. This continuous process depends on a sufficiency of the vitamin. The rate of formation of visual purple after exposure of the retina to bright light depends on the vitamin A available. The increasing ability to see in dim illumination after exposure to bright light is "dark adaptation"; the measurement of this function is the basis for methods used for indirect evidence of vitamin A deficiency. By this method normal controls give initial biophotometer readings of 0.50 millifoot candles or less. The average reading of 13 controls was 0.32; that of 79 patients with rheumatoid arthritis was 0.78; readings in

the 79 cases of rheumatoid arthritis were normal in 35 per cent, between 0.50 and 1.00 (borderline or subnormal) in 35 per cent, between 1.00 and 1.50 (moderate deficiency) in 21 per cent, more than 1.50 (severe deficiency) in 9 per cent. Those patients who were notably deficient in vitamin A did not have xerophthalmia or keratomalacia; one had night blindness. Normal adults require 2,000 to 4,000 units of vitamin A daily; average well rounded diets contain 6,000 units but many of these arthritics required 4 to 11 times that amount (25,500 to 68,000 supplemental units of vitamin A as halibut liver oil) to maintain normal dark-adaptation curves. It is not clear whether this increased need for vitamin A represents increased utilization, decreased absorption or an inactivation of the vitamin (Hall, Bayles and Soutter).

2. Vitamin C. The plasma content of ascorbic acid of only one of Jacques' 48 patients with rheumatoid arthritis was normal (0.7 to 0.9 mg. per 100 c.c. of blood); in the remaining 47 it was subnormal (0.37 to 0.68 mg.; average 0.42 mg. per 100 c.c.). (In 18 of 20 cases of osteo-arthritis levels were more than 0.7 mg.; average 0.92 mg.) Secher also reported that his "patients with rheumatic arthritis generally had no ascorbic acid in the blood," an abnormality noted in other diseases as well. Secher noted abnormal sugar tolerance curves ("decreased tolerance for sugar") in cases of arthritis and also other diseases "which had only one feature in common with arthritis; no ascorbic acid in their blood." But when sufficient ascorbic acid was given to restore the normal ascorbic acid level in blood, sugar tolerance curves became normal. "It may therefore be assumed that the cause of the abnormal blood-sugar curves described by Pemberton [in arthritics] is a deficiency of ascorbic acid, and it is on this deficiency that the shape of the curves depends."

[Secher gave few figures to support this important conclusion. We will await with interest further studies on the correlation between deficiency of ascorbic acid in blood and abnormal sugar tolerance curves.—Ed.]

Intestinal Toxicosis. Wiltsie upheld the idea that streptococci from primary foci invade the body to form secondary foci in colon, liver and elsewhere.

[This report combined many quotations of others and much hypothesis but little or no evidence to support its hypothesis.—Ed.]

Factor of Endocrine Abnormality. For reasons which cannot be adequately reviewed herein Helfet stated his belief that the pathogenesis of rheumatoid arthritis may involve abnormal parathyroid function, or "secondary hyperparathyroidism." He noted certain features (advanced osteoporosis, "bone changes not dissimilar to fibrocystic disease," passage of a calcium phosphate stone) present in two cases of rheumatoid arthritis and cited the reports of Oppel (1926), Ellis (1927), Schkurov (1935) and Leriche (1935), some of whose reports we have previously criticized.[3, 4] Helfet admitted that there is little biochemical evidence that the parathyroid gland plays a critical rôle in rheumatoid arthritis.

Psychogenic Factor. McGregor gave case-examples in which the onset or flare-up of rheumatoid arthritis bore a close time relationship to some emotional episode.

Many arthritics are emotionally unstable before the onset of their disease. Considering the profound changes in one's outlook on life which arthritis may produce, modifications of personality may be expected. But often some emotional crisis seems actually to precipitate the disease. Among several reasons for ascribing etiologic importance to psychologic factors are two: (1) the potency of the mind in producing and maintaining (for various reasons, e.g. sympathy, sickness benefits) such symptoms as pain and stiffness; (2) the fact that emotional conflict can disturb the endocrine and the vegetative nervous systems. But "there is nothing conclusive in establishing a relation between emotional events and attacks of rheumatism unless it can be shown that such a relation is peculiar to the disease in question. At present this has not been done." Meanwhile, regardless of whether emotional disturbances among arthritic patients are of primary or secondary etiologic importance, many will not respond adequately to treatment until their psychologic problems have been attacked properly.

Conclusions on Etiology. In Italy "the prevalent opinion is that rheumatoid arthritis is a true infectious disease: the fact that the causative agent has not yet been found does not mean that it does not exist." [464] According to Pemberton and Scull the streptococcal antibodies present in the serums of patients with rheumatoid arthritis are "not to be dismissed from consideration, but their etiologic importance must be interpreted conservatively as nonspecific until more direct evidence is at hand." Impressed by the ameliorating effect of jaundice and pregnancy on rheumatoid arthritis Osgood concluded that "the chances are better that the unknown etiologic or X factor which we know exists but which we have thus far been unable to discover will prove to be a biochemical rather than a bacterial factor."

[Obviously the cause of the disease remains unknown.—Ed.]

Relationship between Rheumatoid Arthritis and Other Diseases

Rheumatic Fever. Some physicians have used the similarities between the histologic structure of the nodules of rheumatic fever and rheumatoid arthritis as evidence that rheumatic fever and rheumatoid arthritis are closely related conditions. This view was not supported by the study of Bennett, Zeller and Bauer.

Still's Disease. This will be discussed in the section on "Still's disease."

Treatment of Rheumatoid Arthritis

General Remarks. The attitude toward treatment which physicians and patients must have was defined by Chaney, Hench, Horder, Pemberton, and Westcott.

Physicians must discard the idea that "nothing can be done for chronic arthritis." Too many physicians approach their arthritic patients with this wrong frame of mind: they are whipped before they start and the patient often senses it. The overwhelming experience of those who really try to do something for these patients refutes such a pessimistic notion. But physicians must realize that there is no rapid sure cure for the disease and that no one remedy or combination of remedies

is always effective. Treatment based on one hypothesis alone (e.g., the infectious or the metabolic hypothesis) will almost surely fail. He who concentrates on a single remedy (vaccine or diet) is likely to become a faddist. Physicians should treat each patient as an individual problem, rely on procedures of known value and avoid the hasty use of new "cures." These "cures" are much more valuable to their manufacturers than to the patients who use them. Most highly recommended "new remedies" have been shown in time to be of limited or no value. The disease is not cured by a "bottle of medicine" for internal use and a liniment for external use. The physician should select remedies to fit the patient as well as the disease and should subject the patient only to those measures which the stage of his disease and his psychology, constitution and finances warrant.

Patients must also have a definite understanding of just what can and what cannot be done. Some patients have a maximum of expectation and a minimum of tolerance toward their physician. Others have a minimum of expectation and a maximum of suspicion. The patient must possess confidence in his physician and a certain optimism toward therapy. He must not expect a rapid cure. He cannot placidly munch pills or passively accept a vaccine to the exclusion of other measures. He must make positive efforts on his own behalf. He should accept an initial selection of conservative measures of known value. He must not expect that under treatment his condition will improve constantly and without interruption; he must expect some variability in his response to therapy. He does have a right to expect therapeutic versatility on the part of his physician, and he should expect changes in treatment if and when necessary. But he must not expect some new, diverting treatment every little while. To give any plan of treatment a fair chance he should accept it for at least four months, and the final evaluation of any treatment should not be made for at least two years.

Management of Foci. Credit for being the first to cure rheumatic or other pains by removing infected foci has been given variously to Hippocrates,[93] Ashur-bani-apal, a seventh century Assyrian king,[435] and Benjamin Rush.[70]

[Many recent writers have cited Hippocrates as having relieved two patients with rheumatism by extracting teeth, but not one of these writers has given the original reference. One of us, P. S. H., has tried repeatedly but vainly to find this reference in available translations of Hippocrates and by correspondence with those who have passed this citation along. Can any reader supply the reference or is Hippocrates, once more, being credited with something he did not do?—Ed.]

Arguments against the practice of removing infected foci are becoming more vigorous.[232, 435, 469] Two reports in particular were critical of the theory of focal infection as a cause of rheumatoid arthritis. Haden wrote: "It seems more and more evident to critical observers that focal infection is concerned only as an influencing factor in rheumatoid arthritis and is not the point at which a specific organism causing the arthritis is harbored. If the infection does get in through the throat, it seems to do so after removal of tonsils as well as before. It is possible that focal infection is more important early in the course of the disease than it is later." Haden considered preceding or coincident infections, especially with hemolytic streptococci, the most frequent precipitating factor. "It seems possible that a toxic protein may be the immediate source of the joint inflammation such as is known to occur in the arthritis of serum sickness."

Even more critical was the report of Reimann and Havens on "the case against indiscriminate removal of teeth and tonsils" in rheumatoid arthritis and other diseases supposedly caused by infected foci. Although tonsils are often removed as a matter of routine, there is no evidence of the specific value of the procedure in rheumatoid arthritis. No studies have been made with adequate controls, and too little is said of the actual harm which tonsillectomy may do. Summarized was cumulating evidence "throwing grave doubt on the practice of removing tonsils or teeth in the hope of preventing the onset or influencing the course of rheumatoid arthritis." With others Reimann and Havens have become skeptical of the bearing of focal infection in this disease. They concluded that harmful effects from tonsillectomy occur more often than is generally known: 85 deaths occur annually as a result of tonsillectomy on children less than 15 years of age; in one group of cases cited, 57 per cent of deaths from anesthesia occurred during tonsillectomy on children; from 40 to 60 per cent of pulmonary abscesses follow tonsillectomy and other oral operations; tonsillectomy and alveolectomy may lead to temporary bacteremia and bacterial endocarditis. The writers concluded that the experience of 25 years had not proved the value of removing infected foci in rheumatoid arthritis. The procedure should be recommended only in "exceptional cases when evidence of actual local disease is present and its relation to remote or systemic disease probable." Even then the removal of local infections in the hope of influencing remote or general symptoms must be regarded as an experimental procedure not devoid of hazard. Many foci of infection heal after the patient recovers from systemic disease, or when the general health is improved with hygienic and dietary measures.

[This critique would have been more forceful if it had included original data, case reports, statistics, and so forth on the author's own failures and disasters following removal of infected foci. The paper comprises chiefly a compilation of the opinions of others unfavorable to the theory of focal infection. As such it is a valuable résumé, but it is regrettable that the writers made no attempt to marshal convincing evidence of their own. —Ed.]

Some of those who are now belittling the theory of focal infection (e.g., Cecil, Haden) were formerly among its staunchest advocates. [Their frankness in explaining the reasons for their about-face is commendable and lends considerable weight to their current views. But if they were wrong once they may not yet be entirely right.—Ed.] Many physicians may react to these "conversions" as did Pemberton who, to say the least, has never been accused of being an enthusiast concerning the removal of infected foci, and who has for years sought to restrain the medical profession's enthusiasm for the theory of focal infection. Pemberton now writes: "It is a rather curious commentary upon the present situation that the writer now finds himself in the position of endeavoring to stem the growth of such an iconoclastic attitude as would sweep away all consideration of the rôle that focal infection plays in arthritis. The pendulum of medical opinion seems always to be swinging from one extreme to another. We are [now] in danger of doing injustice to hosts of arthritics through shortsighted neglect of the limited but definite rôle of focal infection in this and in other diseases."

[All of which probably leaves most of us about where we have been.—Ed.]

Haden agreed that definitely infected foci should be removed "on general principles." This should be done in mild cases as early as possible but in the more severe cases only at the optimal time, that is after the patient is

properly "built up," after "physiologic equilibrium" has been more nearly restored by a preliminary program of rest in bed, dietotherapy and other measures.[22, 232, 447] There are "rare severe cases in which the ravages of focal infection are so marked that no option remains but to proceed at once with whatever measures may be necessary."[447] It is the duty of the internist, not the "focal specialist" alone, to evaluate foci and determine how and when they shall be treated. Pemberton has seen "many instances" in which premature removal of foci precipitated a serious flare-up.

[Not a few writers have made such statements. It is unfortunate that statistics thereon are rarely if ever given.—Ed.]

1. Teeth. Treatment of gingivitis is as important (if not more so) as the removal of infected teeth.[22, 34, 447] Infected teeth and pulpless teeth with apical infections should be removed.[22, 34] Some [232, 469] considered the removal of "questionable teeth" unwise: "decreased density about a dental root is no more proof of infection there than is increased density in the case of nasal sinuses. The cultivation of bacteria from teeth gives little information since the bacteria usually present have no proved relation to the arthritis." Bach considered the removal of such teeth justified in progressive arthritis. "It is the exception rather than the rule to note dramatic improvement after removal of dental foci; nevertheless they should be removed to 'lessen the patient's load' and not to cure the arthritis per se."[129]

2. Tonsils. Methods to determine tonsillar infection [22, 443, 469] and the occasional harmful effects of tonsillectomy [469] were noted. Infected tonsils of young patients should be removed, but the tonsillar infection of older patients and those who refuse tonsillectomy can be successfully treated by irrigations, expressing secretions and applying germicides according to Bach and Beir. Adenoids may be as infected as tonsils.[22] According to Bach infected lingual and pharyngeal lymphoid tissue is the cause of throats which are "scratchy" even after tonsillectomy. Beir considered neglect of infected lingual tonsils and adjacent lymphoid tissue the greatest cause for failure to relieve patients by focal removal. Of his 18 patients with rheumatoid arthritis whose tonsils were removed 44 per cent were "cured," "all others were greatly improved."

3. Sinuses. Methods for determining sinusitis were described. Roentgen therapy is sometimes successful.[22]

4. Gall-bladder. If infection of gall-bladder is definite in cases of arthritis, gall-bladders should be removed, otherwise medical treatment is indicated (low fat diet, choleretics, e.g., decholin, repeated drainage, autogenous vaccines). Under such treatment gall-bladders may become normal, according to Willard and Strawbridge.

[They give no statistics as to the improvement of arthritis thereby; one case only was cited in which joints and gall-bladder cleared up under such therapy.—Ed.]

5. Intestines. Two writers [22, 605] believed that intestines may act as foci. But cultures of stool rarely give useful information.[22]

6. Prostate. The determination of genito-urinary infection was discussed.[22, 606] Prostatitis, "common secondary focus," should be treated especially in cases in which joints are temporarily aggravated by prostatic massage incident to examination.[22]

7. Female Pelvis. The conservative and radical therapy of pelvic infection was discussed.[22] Pelvic heating by local diathermy was recommended.[146]

Results of Focal Removal. As usual practically none of the advocates of focal removal gave statistics on results. Pavey-Smith wrote: "If an infected tonsil is removed within six months of the onset of the rheumatism a com-

plete cure is probable." Beir claimed to have cured 44 per cent of his patients by treating the lingual tonsils. It is difficult indeed to share this enthusiasm. Generalizations do not settle the argument.

Vaccines, Antigens, Filtrates. The year's literature revealed few protagonists of vaccine therapy. Autogenous vaccines of alpha hemolytic streptococci were used by Hindley-Smith [268]: there were "few cases" in which results were not successful. [No statistics given.—Ed.] But autogenous vaccines according to Small are in each case an untried product which adds one more variable to the procedure. He favored the use of stock vaccines [presumably of his indifferent streptococci (Small, 1929).—Ed.] given in microdoses of only 10 to a few hundred organisms, not thousands or millions thereof. When a patient is doing well dosage must not be increased [no statistics on results given—Ed.]. One hundred patients with "chronic arthritis" [types not stated—Ed.] were given by Schallig staphylococcus-streptococcus undenatured bacterial antigen: 65 per cent were "completely relieved" by 10 weeks' treatment; 28 per cent obtained a "favorable result" within 25 weeks, "only seven patients failed to benefit."

To others results of vaccine therapy have been "uniformly disappointing" [454] or "disturbingly confusing"; the reports were less "rosy" in direct ratio to the carefulness of the investigator.[435] Their value has been unduly emphasized by those who regard the arthritic patient as "a victim of a spray of streptococci." [447] Certainly vaccines are not "specific." [232, 258, 382, 464, 507] Strong evidence suggests that the value of vaccines in arthritis is chiefly from the psychologic effect of the injections. Sidel and Abrams gave a polyvalent streptococcal vaccine to 25 patients with rheumatoid arthritis; 68 per cent improved. But injections of saline solution improved 72 per cent of 33 patients with rheumatoid, and 86 per cent of 64 patients with osteoarthritis. Margolis and Eisenstein questioned 83 members of the American Rheumatism Association: of these only 59 stated that they used vaccines for rheumatoid arthritis. Many now use vaccines much less often than previously. About 60 per cent of those who used vaccines considered them beneficial, but less than 50 per cent of patients are helped thereby. Margolis and Eisenstein no longer use vaccines: "vaccines give the patient a false sense of security on which he may rely too much." One writer [258] published his code for the use of vaccines in rheumatoid arthritis: the physician should never claim that the vaccines are specific or will "cure" the patient; the cost of such therapy should never be burdensome; vaccines should never be relied on alone or used as a form of "occupational therapy" just for something to do. He who breaks this code is in danger of being considered a "vaccine racketeer."

Foreign Proteins. Protein shock by means of triple typhoid vaccine aims at stirring up the patient's immunity mechanism "and hoping for the best." [133] Such therapy was considered useful in selected cases.[133, 232, 258] Straus preferred intradermal injections of lactalbumin.

Bee Venom. Of 50 patients with "chronic arthritis" (30 infectious, 15 menopausal, 5 traumatic) given bee venom by Goldberg, 60 per cent were "definitely benefited," more so than were 22 patients given 40 to 60 grains of salicylates daily. Others reported good results in one case each.[378, 415] Hill considered bee venom of no definite value; it is "a counterirritant and probably nothing else."[596]

Cobra Venom. Macht (1938) recommended the use of cobra venom to relieve pain in certain conditions including arthritis. Steinbrocker and colleagues gave such injections to 13 patients with rheumatoid arthritis: 11 received "slight to moderate" relief; two were unrelieved. Of nine control patients with rheumatoid arthritis given saline injections, none were improved.

[This contrasts with the report of Sidel and Abrams who improved 72 per cent of 33 rheumatoid patients with saline injections. It shows how difficult it is for even the fairest investigator to exclude the personal equation when evaluating any remedy for this disease. It is probably not unfair to say that Sidel and Abrams were of a mind to show that injections of saline solution were as good as vaccines (i.e. that vaccines were no better than saline), whereas Steinbrocker and his associates were convinced that injections of saline solution were valueless compared to cobra venom. These attitudes may have unconsciously influenced the interpretation of the results.—Ed.]

Diet. There is no specific diet. Scull condemned "the bizarre dietary measures based on doubtful premises and exploited in uncritical quarters." The low carbohydrate, high vitamin diet was discussed.[50, 133, 232, 435] The incidence of food allergy among rheumatic patients is not significant.[493]

Vitamins. Patients with rheumatoid arthritis, like those with certain other diseases, often possess subnormal amounts of vitamins in their plasma. These deficiencies are not specific nor of etiologic importance. The supplemental use of vitamins readily corrects the plasma deficiencies but has not significantly affected the joints. There is no "antirheumatism vitamin." "We shall need soon a little debunking of vitamin cure-alls" (Osgood). Of course patients should secure their daily basal requirements: at least 6,000 international units of vitamin A, 250 international units of vitamin B_1 (0.75 mg. of thiamine hydrochloride), 300 international units (100 mg.) of ascorbic acid.[493]

1. Vitamin A. The susceptibility of rheumatic patients to upper respiratory infections may represent a deficiency of vitamin A.[493] The deficiencies noted by Hall, Bayles and Soutter were readily corrected with doses of 25,500 to 68,000 U. S. P. units daily but these doses did not alter the arthritis.

2. Vitamin B. Supplemental doses were recommended unenthusiastically.[419, 503]

3. Vitamin C. To 47 rheumatoid patients with low concentrations of ascorbic acid in plasma Jacques gave 100 mg. by parenteral injection daily for one week and 300 mg. by mouth daily for one month. Plasma deficiencies were corrected but no marked effect on joints was noted. Muether's experience was similar. Secher claimed that by giving ascorbic acid he could restore blood sugar tolerance curves to normal and minimize toxic reactions to chrysotherapy, but he made no claims that joints were improved by the vitamin per se.

4. Vitamin D. Muether's results with vitamin D (type not stated) were "most unconvincing"; he considered the use of large doses dangerous and irrational as did Abrams and Bauer.[6] But Snyder and Squires claimed that there are notable differences in toxicity and therapeutic potency in vitamin D (ertron) as made by the Whittier process and other vitamin D products (viosterol, drisdol, calciferol) prepared by ultraviolet radiation of ergosterol (as used by Abrams and Bauer).

[Further evidence is needed to support this claim.—Ed.]

Snyder and Squires gave from 100,000 to 600,000 (average 300,000) U. S. P. units of ertron daily for four to 18 months to 12 patients with rheumatoid arthritis (and to 11 with osteo-arthritis) unrelieved by other measures. Results were excellent in four cases, good in four, slight in four with rheumatoid arthritis (excellent in one, good in five, slight in three and absent in two with osteo-arthritis). No serious toxicity occurred. It was suggested that the products used by Abrams and Bauer[6] and others might have derived their toxicity from small traces of toxisterol therein. Estimations of blood calcium, phosphorus and sedimentation rates were made before and after treatment, but changes therein could not be correlated with the degrees of improvement noted.

[Snyder and Squires admittedly studied no control series of patients treated with other forms of vitamin D. But other writers have also only used one favorite form. Of the cases of Snyder and Squires sedimentation rates dropped notably in only two, slightly in four, and rose in six, sometimes notably. This suggests that a fundamental error in the disease was not corrected despite some clinical improvement.—Ed.]

Additional intestinal treatment.—Colonic irrigations were advocated by only three physicians.[22, 387, 605] Wiltsie insisted that the failures of others were due chiefly to improper technic for such irrigations. His "improved method" was described. He considered implantation of acidophilus cultures useless as "this does not influence streptococci, the organism usually responsible for the disease" [not proved—Ed.]

Endocrines. Cortin, 3 to 5 c.c., was given by Watson intramuscularly weekly to 12 patients with "chronic nonspecific arthritis." Elevated serum phosphatase values were reduced to normal and "more or less pronounced clinical improvement" occurred. When treatment was discontinued [after an unstated time.—Ed.] phosphatase levels rose and articular symptoms increased. Desoxycorticosterone acetate did not produce similar results.

[Details were meager.—Ed.]

Estrogen was given by Cohen, Dubbs and Myers to 17 patients with rheumatoid arthritis alone, and to six with rheumatoid arthritis and osteo-arthritis. Daily, later weekly, intramuscular injections of 10,000 to 100,000 international units were given. Total dosage varied from 50,000 to 850,000 international units. Of these 23 patients 12 noted "distinct improvement in joint symptoms," three improved some and then relapsed, seven were not relieved and one became worse. Those who had menopausal symptoms noted relief thereof. Twelve additional patients with rheumatoid arthritis but without any menstrual disturbances received 50,000 international units daily for 7 to 21 days without relief. Unless patients with rheumatoid arthritis also have disturbed menstrual function, little benefit is to be expected from estrogen therapy. Such poor results may be due to inadequate dosage, according to Dunn who recommended giving 20,000 to 30,000 rat units (100,000 to 150,000 international units) every third day for nine days

to arthritic patients with symptoms of menopause. Dunn also recommended the use of thyroid in "arthritis" with hypothyroidism.

[No detailed results were reported. The writer was not specific as to what types of "arthritis" were treated and as to whether the symptoms relieved were articular or menopausal. It would appear that only menopausal symptoms were relieved.—Ed.]

Miscellaneous Medicines. Haden still considered neoarsphenamine (0.3 to 0.4 gm. twice weekly for three to five weeks) the most valuable drug of all. "In order to reduce the intake of phosphorus and thus remove the stimulus to the overproduction of parathormone" which he considered a possible cause of rheumatoid arthritis Helfet gave aluminum acetate (average dose, 1 drachm of a 2.5 per cent solution 4 times a day for several weeks) to 15 rheumatoid patients. No ill effects were noted; overdoses can produce rickets. Results were "encouraging." Of the 15 patients 9 were "greatly relieved." No significant roentgenographic or biochemical changes were noted.

[Relief was noted by 9 of 15 patients, i.e., 60 per cent. Is this "the inevitable 60 per cent" who improve under almost any treatment? Further studies will be awaited with interest. The author admitted that "the theoretical basis for treatment by this means was not definitely established." In the gastrointestinal tract aluminum would precipitate phosphorus and thus interfere with its absorption. The continued administration of aluminum might produce a deficiency of calcium and phosphorus. —Ed.]

Hematonics: Transfusions. To combat hypochromic anemia ferrous sulfate (3 grains three or four times daily) was given. This will fail if anemia is from faulty utilization of iron (rather than from faulty absorption); if so, transfusions (two or more, a week apart) may be helpful.[183, 232]

Those Other "Remedies": Pharmaceutical Step-Children. Causalin, which contains aminopyrine and which has been condemned previously [5, 6, 7] caused another death, that of an arthritic woman who took about 90 capsules in one month; agranulocytosis (leukocytes down to 600 per cubic millimeter) developed.[47] Aciform II, also previously condemned,[7] was given by Scully to seven patients with rheumatoid arthritis. Results were "complete recovery" in one, "marked improvement" in three, little or no improvement in three. These patients also received hydrotherapy and aspirin [which probably caused the relief, not the aciform—Ed.].

Sulfur Preparations. Studies by Freyberg, Block and Fromer demonstrated conclusively that there is no rationale to this treatment; in rheumatoid arthritis no primary disturbance of sulfur metabolism exists. Colloidal sulfur in small or large doses does not significantly affect the disease.

Colloidal sulfur (sulisocol) was given, generally intravenously, by Abrams and Bauer to 14 patients. Total doses were generally 310 to 370 mg. within two months; three patients received large doses totalling 1,080 to 2,980 mg. No toxic reactions occurred. Transient subjective improvement was noted by some patients, but none improved objectively and sedimentation rates of the majority were not altered significantly. Of the members of the American Rheumatism Association questioned by Margolis and Eisenstein more had abandoned sulfur than were using it. Results noted during sulfur therapy are either psychogenic or from spontaneous remissions.

Chrysotherapy (Gold Salts). The use of gold salts is now one of the most interesting and contradictory features of the study of rheumatoid arthritis. Detailed analysis of results in 105 American cases [165, 209, 565] and 60 British [175] appeared, also comments, without statistics, on the treatment in more than 200 other American cases.[102, 382, 454]

1. Indications. Rheumatoid arthritis, Still's disease and psoriatic arthritis are considered amenable to chrysotherapy; in ankylosing spondylitis and osteo-arthritis results are debatable [165, 503]; chrysotherapy is not useful in fibrositis or the specific arthritides.

2. Contraindications. These remain as stated in previous Reviews but they were listed again.[17]

3. Results. Phillips, first American physician to report (1936)[4] on chrysotherapy for rheumatoid arthritis, originally considered it of doubtful value; having since reduced dosage to lessen toxicity, he [454] now regards it as reasonably safe and the only remedy which will notably improve sedimentation rates. He gave no detailed results, but cited an excellent response in a representative case.

Ninety cases were divided by Ellman, Lawrence and Thorold into three equal groups: in group 1 solganol B was given intramuscularly in " large doses " (200 mg. weekly), in group 2 in " small doses " (100 mg. weekly), in group 3, the control group, weekly injections of sterile almond oil were given. Treatment was continued for nine months; two courses were given, separated by an interval of six weeks. In giving results the term " rendered inactive " was defined as the patient being relieved of all subjective pain; if limitations of motion were present they were painless and sedimentation rates became normal. Results were as follows in the three groups of cases respectively: disease was " rendered inactive " in 47, 27 and 3 per cent; " improved " in 14, 20 and 22 per cent; condition was unaltered in 2, 1 and 6 per cent; worse in 0, 1 and 1 per cent; there was measurable reduction in articular swelling in 66, 59 and 32 per cent; sedimentation rates became normal in 77, 37 and 13 per cent. Toxic reactions occurred in groups 1 and 2 respectively thus: stomatitis in eight cases and one case; dermatitis in eight and five cases; agranulocytosis (fatal) in one case in group 1; jaundice in one case in group 1. In summary " large doses " produced many more good results and also more toxic reactions than did small doses; although 25 per cent of the controls improved, no consistent or notable effect on symptoms or sedimentation rates resulted from injections of almond oil.

Results at the Brooklyn Hospital were reviewed by Tarsy. A previous series of cases was treated by his colleague, McKenna (1936).[399] Not noted in our Fourth Review, details are given now. Fifty-two patients each received three courses of myochrysine, 2.2 gm. each course [a rather high dose—Ed.], with an interval of six weeks between courses. More than 50 per cent of the patients developed toxic reactions, but " startling clinical improvement " was noted by the 25 patients able to tolerate the gold. Despite good results McKenna concluded (1936) that chrysotherapy was hazardous, often helpful but not curative and not safe enough for general use. De-

termined to use smaller doses than McKenna, Tarsy reopened the subject, giving to 22 patients (including five with rheumatoid spondylitis) three to five courses of gold salts of 1 gm. each (weekly doses generally 50 mg., occasionally 25 mg.). "Great improvement" was noted by 12 (55 per cent). Tarsy considered gold as "one of the most valuable agents" for this disease, "very toxic but one which may achieve brilliant results."

Myochrysine has been used by Cecil in "over 200 cases"; his early results were "discouraging"; recent results have been more impressive. [No details given—Ed.] He noted "a few remarkable recoveries" and many other cases in which "improvement was quite striking," especially in early cases. In two cases German and King noted good but not dramatic results. Sherwood who used gold sodium thiosulfate in small doses (10 mg. not oftener than twice a week) considered gold useful in chronic cases, but symptomatically ineffective in "very acute cases" with leukocytosis and in relatively quiescent cases with normal sedimentation rates. [No details given. —Ed.] Results (not detailed) in 51 cases of Margolis and Eisenstein were "very satisfactory."

4. Dosage. Secher continued to use large doses, much larger than others; he gave single doses of sanocrysin of from 25 to 100 centigrams (250 to 1000 mg.). Maximal single doses were 100 and 200 mg. of solganol B given by Ellman, Lawrence and Thorold, 100 mg. of myochrysine by Cecil. Despite the better results from large doses the tendency to use smaller doses to avoid reactions is increasing. Thus Sherwood gave a maximal dose of only 10 mg. of gold sodium thiosulfate twice a week; Phillips gave an initial injection of 10 mg. (myochrysine), then 11 injections of 25 mg. each as one course; he gave two or three more courses, each a month apart.

5. Toxic Reactions. These can occur after only one dose or not until some time after the last dose.[17, 504] The common toxic reactions (as given in previous Reviews) were listed.[17, 209] Most toxic reactions appear only after sedimentation rates become normal according to Ellman, Lawrence and Thorold: in 96 per cent of their 25 cases of gold toxemia the reactions came then. "It is remarkable how often dermatitis and stomatitis appear if injections [especially of the larger doses] are continued after the sedimentation rate has become normal." [This is not our experience. —Ed.] In addition to the already mentioned toxic reactions noted by them (which included one fatal case of agranulocytosis) they frequently noted transient mild albuminuria without other signs of nephritis. Increased joint pain was often noted but does not warrant interruption of treatment.[504] Sherwood [503, 504] considered hematuria a rare toxic reaction usually seen only in spondylitis; three of the four cases in which he had noted it were cases of spondylitis. Exfoliative dermatitis occurred in three cases (severe in two) of Cecil's 200 or more cases; there were no deaths and no blood dyscrasias. Two severe cases of enteritis (one fatal, one not) from gold were reported. A woman, 47 years old, received, within three weeks, only a few intravenous injections of gold sodium thiosulfate (total 200 mg.); fatal ulcerative enteritis occurred; Anderson and Palmer reported the necropsy data with analyses of the gold content of various tissues. This case resembled the fatal case of Goldhammer (1935). Severe, nonfatal colitis, necessitating 6 months of treatment, affected a woman 32 years old, given nine injections (once weekly) of gold sodium thiosulfate; total dosage was only 310 mg. (Kelly).

In more than 50 per cent of McKenna's 52 cases [399, 565] toxic reactions occurred: transient mild albuminuria without other evidence of nephritis occurred frequently; mild hepatitis with jaundice, in one case; febrile epistaxis, severe in two cases, mild in six or eight; corneal ulcers, in six cases; exfoliative dermatitis, in three cases; milder dermatitis often; fatal cerebral thrombosis, in one case after six injections, each of 50 mg. of myochrysine. Among his own 22 cases Tarsy noted the following

toxic reactions: exfoliative dermatitis in four cases; thrombocytopenia (platelets 120,000) in one; eczematous or maculate dermatitis in two; a fatal cerebral accident in one case six weeks after the last injection and after the onset of a scarlatiniform rash.

Most of the rheumatologists who answered the questionnaire of Margolis and Eisenstein were afraid of chrysotherapy. They reported mild toxic reactions, in 10 per cent, moderately severe in 25 per cent, fatal in 0.8 per cent of cases. One instance of fatal aplastic anemia was noted. One informant wrote, "Used it once, never again." Some physicians were more enthusiastic, but the majority considered chrysotherapy "promising but at present dangerous"; "should not yet be generally adopted"; "not sufficient in results to justify the risk."

6. Treatment of Toxic Reactions. There is no specific antidote; treatment is symptomatic. Sherwood considered time the only remedy for the dermatitis. Purpura results from thrombocytopenia; for the latter Sherwood stopped injecting gold and gave liver extract and vitamin C daily until platelet counts became normal. Dextrose and intravenous injections of sodium thiosulfate, the use of liver extract, calcium gluconate and vitamins A, B, and C were recommended by some but regarded as of questionable value by others.

[We know of no satisfactory treatment for toxic reactions.—Ed.]

7. Prevention of Toxicity. Secher again [6, 498] advised the use of large doses of vitamins A, B and C; since using them he has had no cases of thrombocytopenia and has reduced the incidence of erythema. According to him much "gold toxemia" results not from gold but from ascorbic acid deficiency, not from metallic poison but from "liberated toxins." [Secher gave no statistics and few examples of the value of vitamins. The doses of ascorbic acid given were not noted.—Ed.] Tarsy's prophylactic regimen included viosterol 15 drops daily, calcium gluconate 1 drachm twice a day and intravenous injections of 2 c.c. of ascorbic acid. If itching or vertigo appears, use of gold should be discontinued. [Despite his scheme, toxic reactions affected 37 per cent of his patients, one case fatally.—Ed.] In the presence of bleeding gums or purpura Sherwood stopped gold injections permanently; he considered vitamin C somewhat protective. Liver extract was considered by MacKee and Astrachan of some value in preventing intolerance to heavy metals, including gold.

[Only one instance of chrysotherapy was specifically mentioned. We know of no remedy which will prevent toxic reactions.—Ed.]

Patients under chrysotherapy should have examinations of mouth, skin, urine and blood cells each week, platelet counts and estimations of nonprotein nitrogen of blood every three to four weeks; at first signs of a reaction treatment should be stopped for a month, then resumed with smaller doses.[596] Because the toxic reactions observed by them came almost exclusively when sedimentation rates became normal, Ellman, Lawrence and Thorold stopped injections when rates fell below 12 mm., waited three or four weeks, then gave smaller doses (about 20 mg. weekly). If pruritus occurs, gold therapy should be stopped at once, or exfoliative dermatitis may appear.[503] The best prophylactic is the use of small doses of gold, according to Sherwood [504]; by giving not more than 10 mg. once or twice a week he obtained "very beneficial results," no fatalities and only one reaction necessitating hospitalization.

8. Mode of Action. To study the pharmacology of gold salts, a new method for quantitating gold in urine and blood with the Evelyn photo-electric colorimeter was reported.[54] Some regard gold as a catalyst.[565] Gold sodium thiomalate possesses marked bacteriostatic effects against experimental hemolytic streptococcal infections in mice; a dose of 2 mg. given subcutaneously protected most animals injected with 1,000 times the lethal dose of culture (Dawson and Hobby). Sabin and Warren compared the bactericidal effects of myochrysine and a new compound, calcium myochrysine, on experimental arthritis in mice inoculated with pleuropneumonia organisms.

[How gold salts work in rheumatoid arthritis is not known.—Ed.]

9. Conclusions on Chrysotherapy. Some current conclusions follow. Despite its dangers, it forms "the best means at our disposal for the treatment of chronic rheumatism"; such is the Italian view.[464] It should be used "as a routine for all cases in which the disease shows evidence of a progressive course"; the most suitable dose is still debatable.[175] Although early high hopes have not been fully realized, this remedy is "of greater value than any other single measure."[265] But German and King called it "too dangerous for general use" and Pemberton said, "*Gold is intoxicating* and may cause serious reactions. . . . Use it last, if at all." Westcott and other associates of Pemberton regard gold with "waning enthusiasm," a remedy to be used only in research clinics. Still others took an intermediate position. "The seriousness of the disease justifies its cautious use."[565] According to Cecil, chrysotherapy marks an important advance; it is a "dangerous agent," but "in the hands of an experienced therapist it can be used with considerable benefit." It is "effective but dangerous" according to Sherwood; gold is a lethal drug which easily can cure the disease but kill the patient; the larger the dose, the quicker the result, and the higher the mortality rate.

[We approve the opinion of Osgood that "gold therapy has its seeming triumphs and its possible disasters. If it be carefully controlled it has a better chance to survive than either sulfur or vaccine therapy." But Osgood reminded us of the end results, without the use of gold, reported by Kahlmeter[4]: three years after their dismissal from the hospital 60 per cent of Kahlmeter's patients were back at work. No final evaluation of chrysotherapy is yet possible.—Ed.]

10. New, Relatively Nontoxic Gold Compounds. Convinced that gold salts are beneficial, workers are seeking some new nontoxic gold compound. A new and presumably "comparatively nontoxic" gold compound, aurol-sulfide (Hille), an aqueous solution of colloidal gold sulfide, was given by Driscoll and Markson in varying doses to 51 patients with rheumatoid arthritis: 41 per cent were "definitely improved" (as were 39 per cent of 49 patients with osteo-arthritis). Toxic reactions (nausea and vomiting) occurred in only 2 per cent of their cases.

[These results will have to be revaluated in the light of the recent report of Freyberg, Block and Levey who noted that the absorption and utilization of colloidal gold (aurol-sulfide) is different from that of crystalline compounds (myochrysine, sanocrysin). When colloidal gold was used, the average amounts of gold in plasma and urine were small, even though much more gold was given than when the crystalline forms were used. This may account for the lower toxicity of colloidal gold; also "therapeutic failures are to be expected in those persons whose plasma gold values are very small." It will be remembered that Forestier[3] (1935) stated that colloidal gold is ineffective.

In this and in previous Reviews we have reported the doses of gold as stated by the various writers; these doses have almost always referred to the gold salts and not the actual gold content. Myochrysine (gold sodium thiomalate) contains 505 mg. of gold and 82 mg. of sulfur per gram; that is myochrysine is about 50 per cent gold by weight. When 100 mg. of the gold salt which is commercially sold as myochrysine are

given, really only about 50 mg. of gold are given. Sanocrysin (gold sodium thiosulfate) is 37 per cent gold by weight; it contains 374 mg. of gold and 240 mg. of sulfur per gram. The new gold compound, aurol-sulfide (colloidal gold sulfide—Hille) is 87 per cent gold by weight; a 0.5 per cent solution contains 4.35 mg. gold and 0.65 mg. sulfur per cubic centimeter (i.e., 870 mg. of gold and 130 mg. of sulfur per gram). Thus in comparing the relative toxicity and effectiveness of the various gold compounds it should be realized that some compounds contain only from a half to a third as much gold as others. For comparative purposes it would be best if investigators reported doses in actual gold content. For the present, however, we will continue to report doses as stated in the original references.—Ed.]

More promising is the preliminary report of Sabin and Warren who from a study of comparative toxicity of various gold compounds found that their toxicity (as measured by lethal effect on mice) and their therapeutic value (as measured by their effect on experimental arthritis from pleuropneumonia organisms), were functions of different attributes of the gold compounds. They noted that although "colloidal preparations of gold or of gold sulfide were therapeutically inert," a distinct, though delayed, curative effect followed the use of an insoluble compound, calcium aurothioglycomalate. In mice "the margin of complete safety" was "at least 100 times greater" for this compound than for myochrysine, and the new compound was "about ten times more effective therapeutically" than the latter.

[Clinical and further experimental studies with this compound will be awaited with great interest.—Ed.]

Vasodilators: Histamine; Choline. Histamine diphosphate dilution (1 to 1000) was given subcutaneously (0.1 to 0.6 c.c.) by Muether to 10 patients with rheumatoid arthritis: seven noted increased mobility and diminution of pain. Histamine given subcutaneously is as effective as when given by iontophoresis and much more effective than when applied in ointments. "Histamine will not cure arthritis; it is at best an adjunct." Ointments containing histamine hydrochloride dilate capillaries but constrict arterioles according to Cohen and Rosen; ointments of acetyl-beta-methylcholine chloride dilate both capillaries and arterioles. The latter ointment gave "some measure of relief" to 96 patients with "arthritic pain resulting from circulatory disturbances."

[Type of arthritis not stated. These patients received other treatment besides the vasodilators. Results do not impress us.—Ed.]

Sulfanilamide. This drug is valueless.[382]

Bile Salts, Liver Extracts, Etc. No practical method has been found to reproduce the effect of spontaneous jaundice by giving bile salts, bilirubin, liver extracts, alone or in combination. Hench [256] reviewed his own attempts and those of others. The introduction of bile salts by iontophoresis produced no effect, other than local hyperemia, on "several patients with rheumatoid arthritis (Westcott). Cecil [102] was unable to confirm the impression of Davis [151] that large doses of crude liver extract affected rheumatoid arthritis favorably.

Rest and Motion. "Rest is the hardest but the most important medicine to take." [502] Systemic rest is almost a sine qua non for seriously ill arthritic patients. Preferably this means putting a patient to bed in a hospital. In some cases this is all that is necessary.[447] When rest in bed is

impossible the patient should regulate his activities to permit as much rest as possible. But "body-rest in bed" must be combined with "joint-motion in bed" to prevent contractures by moving each joint through its full range of motion once or more daily.[282]

Physical Therapy. A number of general articles on the indications, contra-indications, methods of application and latest developments of various forms of physical therapy appeared.[103, 265, 289, 334, 336, 337, 339, 341, 387, 404, 502] Especially useful was one by Krusen.[339] Physicians are increasingly stressing the importance of teaching patients methods of home physical therapy: "self help under sound direction." [258, 280, 339]

Simple methods applicable for home use were described.[258, 339] A cheap heating lamp used 365 days a year is of far greater value than some elaborate form of physical therapy which the patient can afford only for a few days or weeks.[106] "I am convinced from long experience that, when patients are properly instructed concerning home massage, much more good than harm will result even though the amateur masseuse cannot hope to approach the skill of the trained technician."[339] Copeman described methods, used by him in the British Expeditionary Force, to provide physical therapy in war hospitals not equipped with electricity.

[They are mentioned later under "Physical therapy and War."—Ed.]

Indications for short and long wave diathermy were discussed.[169] Diathermy provides the most effective source of deep local heat.[336, 340] Diathermy may aggravate acute arthritis or bursitis unless given in small doses.[155, 615, 616] In the treatment of bursae and the more superficial joints Kovacs[333] preferred long wave to short wave diathermy. Some who considered diathermy "useless" for rheumatoid arthritis[28, 82] prefered galvanism.[82]

The newer technic of contrast baths,[339] indications for paraffin baths,[335, 387] various forms of light therapy[341, 387] and hydrotherapy[163, 392] were described. Ultraviolet therapy is contraindicated in presence of fever.[387] The distinct advantages of underwater therapy were stressed.[192, 197, 345, 466]

Spa therapy received constructive criticism. There are more than 300 health resorts in the United States, but they have not had the full support of the medical profession for various reasons, chiefly because of objectionable forms of publicity and frequent lack of competent medical direction,[335, 392] also because of "absurd claims made by hotel managers, bath attendants and even medical directors for virtues of their particular mineral waters."[613] "Quackery and incompetent diagnosis and treatment are almost habitual at these places" (Wyman). Kovacs[335] recommended more effective coöperation between spa organizations and the medical profession to raise spas to the high standards of our hospital system, insuring dependable skilled care for rich and poor. Managed properly, spas have many advantages for rheumatic patients.[520]

Medical schools and hospitals should do more to train students, internes and graduate physicians how best to utilize physical therapy.[136] Approved schools for physical therapy technicians were listed.[137] The University of Minnesota has instituted graduate teaching and continuation study in physical therapy.[426, 427]

Climate. There is not enough certainty as to the influence of climate to justify families to make considerable sacrifices of convenience or of earning power to secure a change of climate (Horder).[280]

Occupational Therapy. Several reports stressed the importance of occupational therapy.[37, 144, 269, 304, 458] Types of exercises suitable for the vari-

ous stages of arthritis and for the specific joints affected were described and specifically grouped by Pattee. Recently the British Army adopted occupational therapy as an approved method of treatment for rheumatic and allied conditions.[280] Approved American schools of occupational therapy were listed.[138]

Roentgen Therapy. Of eight patients given roentgen therapy in "relatively large doses" by Ochsner and Mumford one obtained complete relief; four, "great" relief of pain and stiffness; the appearance of relief was sometimes delayed several weeks. Of 39 cases of "arthritis" in which roentgen therapy was given, Weinberg noted "complete relief" in 13, "improvement" in 26.

[These studies were not controlled; in the second study no attempt was made to clarify the types of "arthritis" treated. More recent, well controlled studies[522, 523] lead to the conclusion that roentgen therapy, although perhaps valuable for rheumatoid spondylitis, is of little more than psychotherapeutic value in rheumatoid arthritis of peripheral joints.—Ed.]

Inhalation of Carbon Dioxide. A "transient, small but significant" decrease in stiffness was noted by 10 patients with rheumatoid arthritis (but not by 10 with osteo-arthritis or fibrositis) who inhaled 10 to 15 per cent carbon dioxide in oxygen for two to five minutes.[365]

Fever Therapy. Few physicians are still using fever therapy. It was considered "helpful in selected cases,"[185] "a reliable measure" when used with other measures[513] and "encouraging" in its results.[580] [How weak in praise is such a remark as results were "encouraging." Swallowing a lot of disappointment, the investigator thereby sadly makes the best of very little.—Ed.] Others regarded fever therapy as of little value.[232, 236, 258] For 75 per cent of 114 patients treated by Solomon and Stecher immediate results were quite satisfactory, but final results, assessed on follow-up, were disappointing: condition of 10 per cent was "improved," of 82 per cent, unchanged, of 8 per cent, worse. Thirteen patients of Margolis and Eisenstein received only very transient relief. Of 57 physicians whom they questioned the majority had abandoned this remedy for rheumatoid arthritis; two fatalities and two near fatalities were noted.

Splenectomy. Recent reports have given results of splenectomy in four cases of rheumatoid arthritis, splenomegaly, adenopathy, leukocytosis or leukopenia, with or without hepatomegaly. One patient noted marked improvement maintained at least five months (Hanrahan and Miller,[1] 1932); another noted only transient improvement (Craven,[2] 1934); both patients died within 18 months after splenectomy (Fitz,[3] 1935). A third patient obtained a "marked" immediate improvement but died of pneumonia 35 days after operation (Loeper, Lemaire and Patel, 1937). The fourth patient noted a gradual but marked improvement (Villaret et al., 1937).

Splenectomy has been done in three additional cases by Bach and Savage with "marked clinical improvement" in two, no postoperative improvement but gradual quiescence of arthritis in the third. Brief reports of the three cases follow:

A female, aged 18 years, had splenomegaly, adenopathy, anemia and leukocytosis. After splenectomy improvement was gradual. A youth, aged 18 years, had adenopathy and anemia but no apparent splenomegaly. Improvement after splenectomy was not notable but 10 months later the arthritis was becoming quiescent. A woman, aged 29 years, had severe rheumatoid arthritis but no splenomegaly, adenopathy or anemia.

are peculiarly amenable to suggestion. Of 33 rheumatoid patients given injections of physiologic saline solution by Sidel and Abrams 72 per cent felt "improved." Similar injections were given as psychotherapy by Phillips in selected cases.

Institutional Care. The advantages of institutional care were again described.[613]

Integration and Coördination of Treatment. So many remedies are recommended for rheumatoid arthritis that physicians find it difficult to decide what to try first and what to leave until last. Two writers[258, 447] listed their therapeutic choices, gave opinions as to the relative value of each remedy and defined their programs I, II, etc. The fact that their selections did not always agree is further evidence that the treatment of this disease cannot be standardized yet; the fact that they (and others) have agreed on the value of certain remedies indicates that there is a basic program of therapy of the value of which there is little doubt.

Prognosis: End Results. No new statistics on end results were published. Such statistics are difficult to collect, largely because of the unpredictable nature of the disease. Remissions and exacerbations occur most irregularly; many remissions are long enough to be interpreted wrongly as "cures" unless follow-up is carefully made.[596] One long-time student of the disease[435] would only say, "we may expect a certain number of cures, a certain number of remissions, a lesser number of exacerbations and an almost negligible number of patients who will not admit that our care has lightened their load." Unfortunately we badly need more definite information on end results; a few statistics previously given herein were repeated by Snyder.

Failures may be the fault, not of the patient or his disease, but of the physician himself who may (1) fail to make a complete diagnosis, (2) not trust his patients' ability to evaluate therapy ("when the patient comes in and tells you that he has been worse since his last treatment, surely that treatment should be repeated with utmost caution") or (3) not be thorough in treatment (Sherwood).[503] Such failures are inexcusable. These patients deserve the best their physicians can provide. Although some are fretful and wearisome, "the courage, patience and fortitude of the arthritic exceeds that of any other patient afflicted with a chronic disabling disease. It is hard to understand how they can bear the pain, disappointments, and long periods of inactivity in silence or more usually with smiles. Many times it is the courage of the patient that has kept his physician from abandoning all hope of improvement" (Wyman).

Still's Disease and "Felty's Syndrome"

[Readers will be interested to know that Sir Frederick Still died just recently in London, aged 73 years.—Ed.]

In Still's disease (juvenile rheumatoid arthritis with splenomegaly, adenopathy, and anemia) the pathologic reactions in lymph nodes and spleen are not specific.[464] Blood cultures from two children who had febrile Still's disease revealed no pleuropneumonia organisms.[485] Results of fever therapy

After splenectomy a slow steady improvement occurred. In the second and third cases the spleen was found at operation to be twice normal size. Splenic amyloidosis was present in two of the three cases.

[We would hardly call the improvement in these cases "marked." Results in these seven cases do not encourage physicians to advise splenectomy and we know of no rationale for the procedure.—Ed.]

Nonsurgical Orthopedic Methods. Most deformities could be prevented if patients had the services of both physician and orthopedist from the onset of their disease. Arthritic patients are prone to adopt the "comfortable position"; too often this leads to disaster.[556] The common deformities and optimal positions for joints with impending deformities were listed.[36, 556] The simple technic for proper splinting was described.[36, 576] A simple devise whereby patients may apply forced flexion to knees was reported.[174] Some[36, 454] favored the use of wedged casts to correct flexed knees and reserved capsulotomy for subluxation of knees.[36]

Technic for manipulation (without anesthesia) of spine[32] and peripheral joints[600] was described.

Surgical Orthopedic Measures. Aspiration of effusions may reduce intraarticular pressure and prevent small subchondral herniations of debris.[199] Injections of oxygen into arthritic joints were considered useful by Henson[262] in preventing adhesions and relieving pain. [Details were too meager to prove the writer's point.—Ed.] Manipulation of joints under anesthesia was considered "dangerous" by some,[36] useful by others.[600]

Indications and contraindications for various orthopedic measures to correct deformities were again discussed.[36, 452]

Synovectomy, performed by Carruthers 34 times on 28 patients with chronic arthritis, chiefly of the rheumatoid type, gave these results: "very satisfactory" in 22, "fair" in two, improvement in six, failure in four. Reviewing 10 years' experience Speed and Smith concluded that best results from *arthroplasty* were obtained by patients aged 18 to 30 years, and when arthroplasty of hips, knees, elbows or jaws was performed. Preliminary results were satisfactory in two cases in which Speed performed an arthroplasty of hip with insertion of vitallium cap. Results with this procedure on hips have been good enough to warrant further trial; final evaluation cannot be made yet.[530] Campbell[92] adopted this procedure (interposition of vitallium plate after arthroplasty) in two cases of ankylosed knees (from acute pyogenic arthritis) with disappointing results. Transplantation of tibial tubercle was recommended by Preston as a supplement to posterior capsulotomy for flexed knees: this permits immediate full active extension of knees. Royle described an operation for *arthrodesis* of knee joints "used for 15 years without a failure"; femur and tibia unite in 12 weeks.

[Number of patients treated not given.—Ed.]

Psychotherapy. Consciously or unconsciously applied, psychotherapy is essential to the successful handling of rheumatoid patients, who are, as a class, fretful, unreasonable, introspective and without confidence in themselves or their physician. Many lack the urge to get well. Institutional or spa therapy gains much of its success because patients are removed from unhappy surroundings and given optimal rest and care.[265] These patients

in two cases of Still's disease were "excellent" in one, less notable in one.[263] Ishmael used fever therapy plus autohemotherapy in 11 cases; "complete remissions" resulted in nine.

[These results are so unusual that we are anxious to know what a late follow-up will show.—Ed]

Relation of "Felty's Syndrome" to Still's Disease. Ravenna cited an Italian report of two cases of "Felty's syndrome" (leukopenic splenomegaly with polyarthritis) and added that most Italian authors do not recognize the autonomy of this syndrome "which has the same characteristics as Still's disease." A similar conclusion was reached by Curtis and Pollard who compared four cases of "Felty's syndrome" (rheumatoid arthritis of adults with splenomegaly, adenopathy, anemia and leukopenia) with four cases of rheumatoid arthritis, splenomegaly and leukocytosis (not leukopenia) and four cases of rheumatoid arthritis without splenomegaly or leukopenia.

In 11 of these 12 cases biopsies of the skin and calf muscle were made, biopsy of the lymph nodes was made in one, examination of spleen, lymph nodes, bone marrow and muscle after death was made in one case to determine whether or not the disease was generalized and whether Felty's syndrome was a clinical entity or just an expected complex of the disease. Patients were adults aged 27 to 67 years with articular changes characteristic of rheumatoid arthritis. Pathologic reactions in spleen, lymph nodes and bone marrow were nonspecific, "the result of a chronic infection." Reactions in skin and muscle of calf were essentially the same in the three groups studied: atrophy of epithelium, fibrosis of corium, increase in interstitial nuclei of muscle fibers, small perivascular infiltrations throughout corium and muscle—an "angiomyositis" indicating a generalized infectious process. Since the pathologic reactions in the cases of "Felty's syndrome" were similar to those in which only rheumatoid arthritis was present or in which splenomegaly was *not* associated with leukopenia, Curtis and Pollard concluded that the likelihood of the various features (splenomegaly, adenitis, leukopenia or leukocytosis) occurring with rheumatoid arthritis is merely a matter of chance. "There is therefore no justification for the segregation of these cases; the use of the term 'Felty's syndrome' should be discontinued." [We share this opinion.—Ed.] They concluded that Felty correctly interpreted the syndrome, the several features being manifestations of one pathologic process caused by a noxa (the unknown cause of rheumatoid arthritis) which simultaneously affects joints, spleen and circulating leukocytes.

Four cases of "febrile hepatosplenomegaly with arthritis" were described.[99] Splenectomy reputedly improved two of three patients with adult Still's disease ("Felty's syndrome") seen by Bach and Savage.

Osteo-arthritis: Degenerative Joint Disease

"Osteo-arthritis" (or "degenerative joint disease") refers, not to a specific disease but to a type of cartilaginous degeneration accompanied by hypertrophic osseous changes. "Primary osteo-arthritis" (primary degenerative joint disease) is that form which develops insidiously and more or less spontaneously in persons more than 40 years of age. "Secondary osteo-arthritis" (secondary degenerative joint disease) refers to hypertrophic osseous changes in joints incident to trauma (acute, occupational, static, chronic trauma resulting from congenital or acquired joint malformation, etc.) or as a secondary (late) manifestation of another type of arthritis (rheumatoid, gouty, suppurative, etc.).